# THE AMERICAN JOURNAL OF PSYCHIATRY

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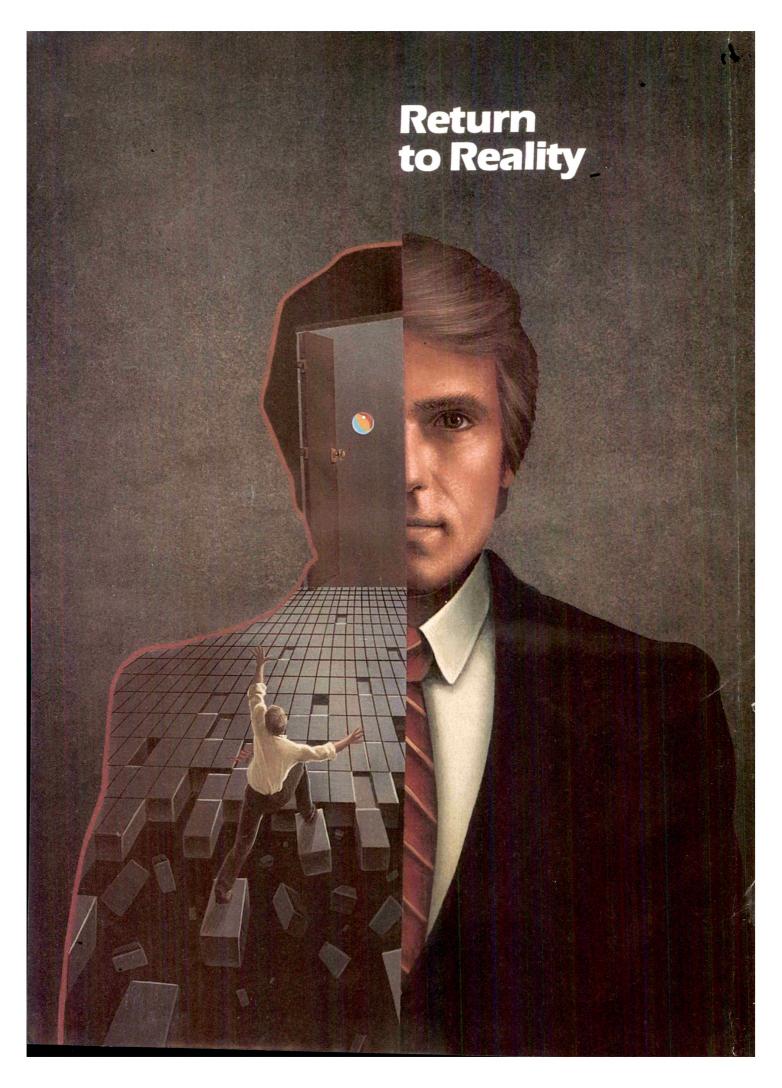
July 1987

In this issue:

A Model for Ethical Problem Solving in Medicine,
With Practical Applications
By Edward M. Hundert

The Legal Basis of Forensic Psychiatry: Statutorily Mandated Psychiatric Diagnoses By Joseph D. Bloom and Jeffrey L. Rogers

Official Journal of the American Psychiatric Association



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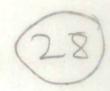
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Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as
duration of treatment and total cumulative neuroleptic dose increase. Much less commonly,
the syndrome can develop after relatively brief treatment at low doses. There is no known
treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment
may suppress signs and symptoms of the syndrome and thereby mask the underlying disease
process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients
who suffer from chronic illness that responds to neuroleptics and for whom alternative,
effective, less harmful treatments are not available or appropriate. In patients requiring chronic
treatment, the minimal effective dose and shortest duration of treatments should be sought.
Periodically reassess need for continued treatment. If signs and symptoms of TD appear,
discontinuation of neuroleptics should be considered. [See PRECAUTIONS.]

Generally avoid using in patients hypersensitive le a. have had blood dyscrasias, jaundicel to

discontinuation of neuroleptics should be considered. (See PRECAUTIONS.) Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehi-cles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

**Precautions:** Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with relations.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, his elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammany tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihyperten-

sive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity, dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive "Stelazine" 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenytletonuria [PKU] test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amend rhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular [extra-pyramidal] reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCI, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders [e.g. mitral insufficiency or pheochromocytoma].

phenothiazines: some adverse effects are more frequent or intense in specific disorders [e.g. mittal insufficiency or pheochromocytoma].

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophorsbinorus insecucides nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urmary retention, miosis and mydriasis, reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregulanties, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatius, asthma, larny geal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema, reversed epinephrine effect; hyperpyrexia, mild fever after large LM, doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy, with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and comeal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines lappa ently due to cardiac arrest or asphyxia due to lailure of cough reflex! has been reported.

Supplied: Tablets, I mg., 2 mg., 5 mg. and 10 mg., in bottles of 100 and 1000; in Single Unit

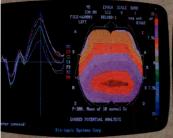
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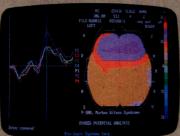
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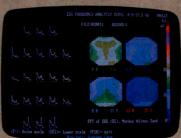
Anyone can make claims. We can demonstrate the system and kind of responsibility it takes to become the world leader in topographic brain mapping.



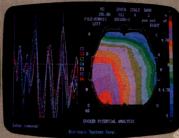
300 mean of 10 normal subjects



P-300 of patient with Morbus Wilson Syndrome



FFT of EEG (EC), Morbus Wilson Syndrome



P-300 of patient with Alzheimer's Disease

# Responsibility

If you want to acquire topographic brain mapping data that will be clinically accepted by your colleagues, you must have a system provided by a company with a proven reputation for responsibility. We will discuss the clinical applications with you which are supported by appropriate research and are available to assist you with diagnosis and treatment. We will talk to you honestly about the ways the BRAIN ATLAS'® can assist you in monitoring psychotropic drugs and provide you valuable information in cases such as schizophrenia, dementia, depression, organic brain dysfunction and alzheimer's disease. At Bio-logic, we always remember that you are the Doctor with the responsibility for diagnosis of patients. Our responsibility is to provide quality systems which will assist you in that diagnosis.

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Before we introduced the first Brain Atlas in April 1984, we had a program in place for the collection and screening of normative data. We will supply you with a quality normative data base which is continuously expanding in number of cases, types of tests and subgroups. Our unique program produces normative data which have been collected in multiple sites according to stringent protocols and anonymously scrutinized by an independent medical review board outside the company. We also provide you with the capability to create your own normative data base. At Bio-logic, our Normative Data Base is an open book. We will share the number of cases we have in each category and explain our data collection/data evaluation process in detail.

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ATLAS EEG MAPPER, BRAIN ATLAS I, BRAIN ATLAS II, BRAIN ATLAS III, BRAIN ATLAS III and the BRAIN ATLAS III PLUS. The BRAIN ATLAS III and the BRAIN ATLAS III PLUS are totally self contain systems and need not be interfaced to an EE machine. All the systems in the series have options available which allow you to tailor the system to fit your specific requirements and budget. Each system is designed to be upgraded as your needs change or as new capabilities are introduced.

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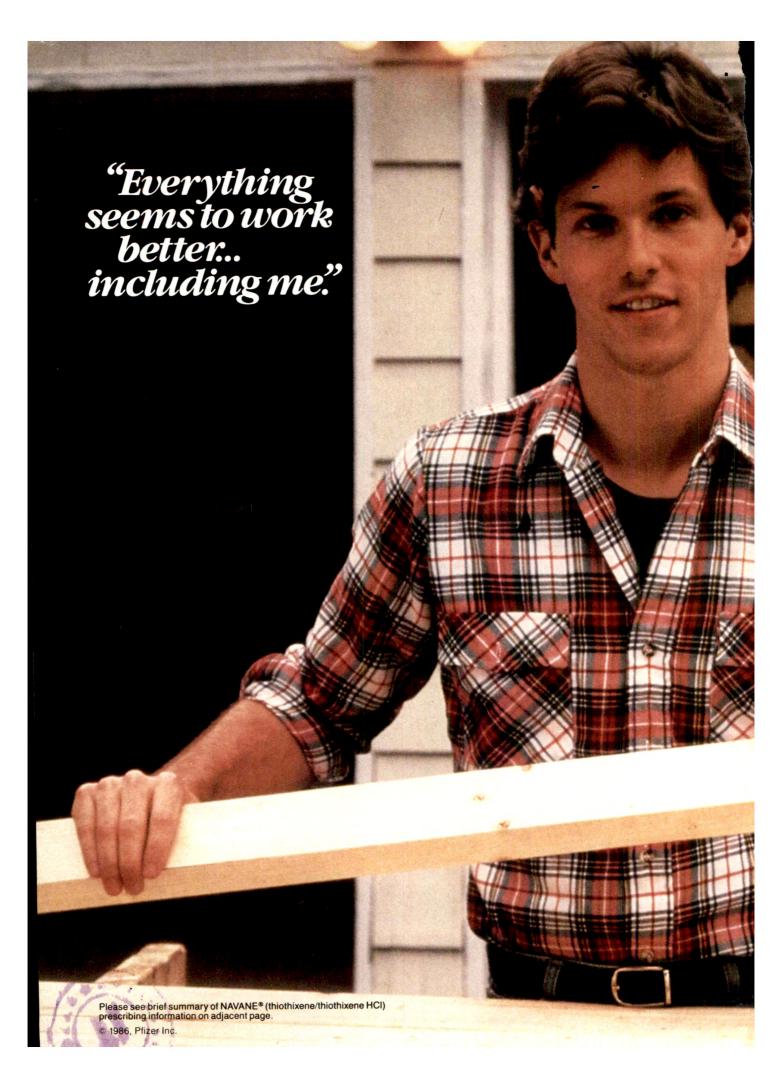
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References: 1 Bressler B. Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971; 12:275-277. 2 DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972; 13:105-108. 3 DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4 Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): The Thioxanthenes: Modern Problems of Pharmacopsychiatry, Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52 5 Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. 6 Data available on request from Roerig.

BRIFF SUMMARY OF PRESCRIBING INFORMATION Navane\* (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg (thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: Tardive Dyskinesia—Tardive dyskinesia, a syndrome consisting of potentially irreversible, invol-untary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dys-

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the pa-tient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the un-derlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety

and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the per formance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible

additive effects (which may include hypotension) with CNS depressants and with alcohol. **Precautions:** An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs

Though exhibiting rather weak anticholinergic properties. Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine len ticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods) Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels: the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neonlasms has been found in rodents after chronic administration of neuroleptic drugs Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association be-tween chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be in

jected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then

only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothix ene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of b sure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently. Hyperreflexia has been reported in inlants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Man agement of these extrapyramidal symptoms depends upon the type and severify. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by

reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis It has been reported that fine vermicular movement of the tongue may be an earth sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been in frequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Altergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been re-ported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontin-uation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia,

hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associated

with miosis, mydriasis, and advnamic ileus. Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to nhenothiazine administration

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders aral administration impractical or even

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Inframuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often

effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of galt, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For

Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/ or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

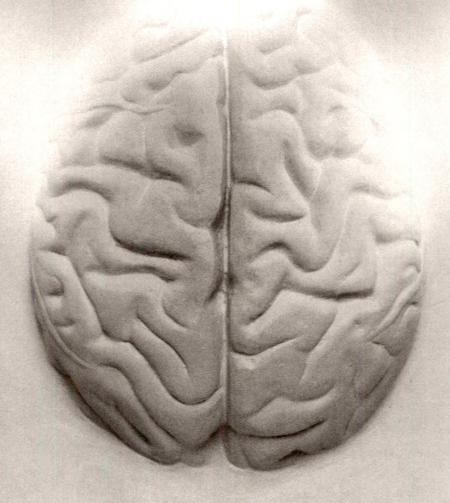
If CNS depression is present and specific therapy is indicated, recommended stimulants include ampheta-

mine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phe-

nothiazine intoxication



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For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

# **SEPTEMBER**

September 4–5, fall meeting, American Association for Social Psychiatry, New Orleans. Contact Carolyn B. Robinowitz, M.D., Secretary-Treasurer, AASP, 1400 K St., N.W., Washington, DC 20005; 202-682-6130.

September 9–12, annual meeting, National Association of Social Workers, New Orleans. Contact Mark G. Battle, A.C.S.W., Executive Director, 7981 Eastern Ave., Silver Spring, MD 20910; 301-565-0333.

September 9-13, Fall Components Meeting, American Psychiatric Association, Washington, D.C.

September 9–13, 2nd International Symposium on Premenstrual, Postpartum and Menopausal Mood Disorders, Kiawah Island, S.C. Contact University of Medicine and Dentistry of New Jersey, Office of Continuing Education, 675 Hoes Ln., Piscataway, NJ 08854-5635; 201-463-4707.

September 11–13, annual conference, Canadian Art Therapy Association, Vancouver, Canada. Contact CATA, Conference Committee, 216 St. Clair Avenue West, Toronto, Ontario M4V 1R2, Canada; 416-921-4374.

September 11–15, annual meeting, Royal College of Physicians and Surgeons of Canada, Winnipeg, Canada. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario K1M 1P4, Canada; 613-746-8177.

September 13–15, annual meeting, Canadian Academy of Child Psychiatry, London, Ontario. Contact J.H. Beitchman, M.D., Program Chairman, CACP, Clarke Institute of Psychiatry, 250 College St., Toronto, Ontario M5T 1R8, Canada.

September 14–17, annual meeting, American Academy of Family Physicians, San Francisco. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

September 16–18, annual meeting, Canadian Psychiatric Association, London, Ontario. Contact Lea C. Metivier, Chief Administrative Officer, 225 Lisgar St., Suite 103, Ottawa, Ontario K2P 0C6, Canada; 613-234-2815.

September 16-20, annual convention, National Alliance for the Mentally Ill, Washington, D.C. Contact NAMI, 1901

North Ft. Myer Dr., Suite 500, Arlington, VA 22209; 703-524-7600.

September 17–18, semiannual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 18–20, child psychiatry examination, American Board of Psychiatry and Neurology, Minneapolis. Contact Stephen C. Scheiber, M.D., Executive Secretary, One American Plaza, Suite 808, Evanston, IL 60201; 312-846-0830.

September 22–25, International Symposium, Brain Acetylcholine: From Preclinical to Clinical Investigations, Taormina, Italy. Contact A.P. Caputi, M.D., Institute of Pharmacology, University of Messina, Piazza XX Settembre, 4, 98100 MESSINA (Italy); 090-712533.

September 22–27, VIIIth European Congress of Child and Adolescent Psychiatry, Varna, Bulgaria. Contact Prof. Dr. Chr. Christosov, Dept. of Psychiatry, Medical Academy, Sofia, 1431, Bulgaria.

September 24–30, II Annual Conference on the Foundations of Behavioral Neurology, Hong Kong. Contact Teresa Santana, Assistant Program Director, So. California Neuropsychiatric Institute, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102, 800-423-9521.

September 26–29, annual meeting, Southern Psychiatric Association, Boca Raton, Fla. Contact Annette S. Boutwell, Executive Director, P.O. Box 10387, Raleigh, NC 27605; 919-821-2226.

September 27–30, annual meeting, Association of Mental Health Administrators, Hollywood, Fla. Contact Weir Richard Kirk, Executive Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

September 27-October 2, annual meeting, American Health Care Association, New York. Contact Paul R. Willging, Ph.D., Executive Director, 1200 15th St., N.W., 8th Fl., Washington, DC 20005-2899; 202-833-2050.

September 28-October 3, annual meeting, Pan American Health Organization, Washington, D.C. Contact Carlyle (Continued on page A14)





The active metabolite of amitriptyline

# All the efficacy of amitriptyline and a favorable side effect profile

Because of anticholinergic activity, PAMELOR (nortriptyline HCI) should be used with caution in patients who have glaucoma or a history of urinary retention.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and falalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor\* (nortriptyline HCI); is started. 2) Hypersensitivity to Pamelor (nortriptyline HCI), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after whocardial infarction.

acute recovery period after myocardial intarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retenion. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Sale use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. In overactive or agitated patients, increased axiety and agitation may occur, in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostilly may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimelidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment, in this regard, it is important that the least possible quantity of drug be dispensed any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: Cardiovascular—Hypotension, hypertension, tachycardia, palpitation myocardial infarction, arrhythmias, heart block, stroke. Psychiatric—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania, exacerbation of psychosis. Neurologic—Numbness, tingling, pares-

thesias of extremities, incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms, seizures, alteration in EEG patterns; tinnitus, Anticholimergic—Dry mouth and, rarely, associated sublingual adentis, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic iteus urinary retention, delayed micturition, dilation of the urinary tract. Allergic—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (general or of face and tongue), drug lever, cross-sensitivity with other tricyclic drugs. Hematologic—Bonemarrow depression, including agranulocytosis, eosinophilia, purpura thrombocytopenia. Gastrointestinal—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abominal cramps, black-tongue. Endocrine—Gynecomastia in the male, breast enlargement and galactorrhea in the female: increased or decreased libido, impotence: testicular swelling, elevation or depression of blood sugar levels: syndrome of inappropriate ADH (antidiuretic hormone) secretion. Other—Jaundice (simulating obstructive), altered liver function; weight gain or loss, perspiration. Itushing; urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue, headache, parolid swelling, alopecia. Withdrawal Symptoms—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion. \*estlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Dealths have occurred with drugs of this class. No specific antidote is known, general supportive measures are indicated, with gastric lavage.



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# Calendar

(Continued from page A10)

Guerra de Macedo, M.D., Director, 525 23rd St., N.W., Washington, DC 20037; 202-861-3200.

## OCTOBER

October 6–11, annual meeting, American School Health Association, Indianapolis. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 7–10, annual meeting, American Academy of Clinical Psychiatrists, Toronto. Contact Robert Budetti, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-460-2675.

October 8–11, annual meeting, American Medical Care and Review Association, Monterey, Calif. Contact Ronald A. Hurst, Executive Vice-President, 5410 Grosvenor Ln., Suite 210, Bethesda, MD 20814; 301-493-9552.

October 9–12, Vth Scientific Conference of the International Federation of Psychoanalytic Societies, New York. Contact Ann R. Turkel, M.D., Secretary-General of the IFPS, 350 Central Park West, New York, NY 10025; 212-831-3400.

October 11–16, annual meeting, American College of Surgeons, San Francisco. Contact C. Rollins Hanlon, M.D., F.A.C.S., Executive Director, 55 East Erie St., Chicago, IL 60610; 312-664-4050.

October 15–17, annual meeting, Canadian Association for Community Living, Washington, D.C. Contact Jacques Peletier, Executive Vice-President, Kinsmen Bldg., York University Campus, 4700 Keele St., Downsview, Ontario M3J 1P3, Canada; 416-661-9600.

October 15–17, annual conference, Canadian Group Psychotherapy Association, Banff, Alberta, Canada. Contact Dr. Edgardo Perez, Dept. of Psychiatry, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9, Canada.

October 15–17, annual meeting, National Association for Retarded Citizens, Washington, D.C. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue "J," Arlington, TX 76006; 817-640-0204.

October 15–18, annual meeting, American Academy of Psychiatry and the Law, Ottawa. Contact Ms. Kathy Smith, AAPL, 1211 Cathedral St., Baltimore, MD 21201; 301-539-0379.

October 17–19, annual meeting, Association of Mental Health Librarians, Boston. Contact Zing Jung, M.L.S., American Psychiatric Association Library, 1400 K St., N.W., Washington, DC 20005; 202-682-6057.

October 18–21, annual meeting, American Neurological Association, San Francisco. Contact Jan W. Kolehmainen, Executive Director, 2420 Pershing Rd., Kansas City, MO 64108; 816-474-5720.

October 18–22, annual meeting, American Public Health Association, New Orleans. Contact William H. McBeath, M.D., M.P.H., Executive Director, 1015 15th St., N.W., Washington, DC 20005; 202-789-5600.

October 18–22, annual meeting, World Medical Association, Inc., Madrid. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 33-50-40-75-75.

October 19–23, annual meeting, American Society for Therapeutic Radiology and Oncology, Boston. Contact John Ciccone, ASTRO, 1891 Preston White Dr., Reston, VA 22091; 703-648-8910.

October 19–25, annual meeting, World Federation for Mental Health, Cairo. Contact Eugene B. Brody, M.D., Secretary General, 1021 Prince St., Alexandria, VA 22314-2932; 703-684-7722.

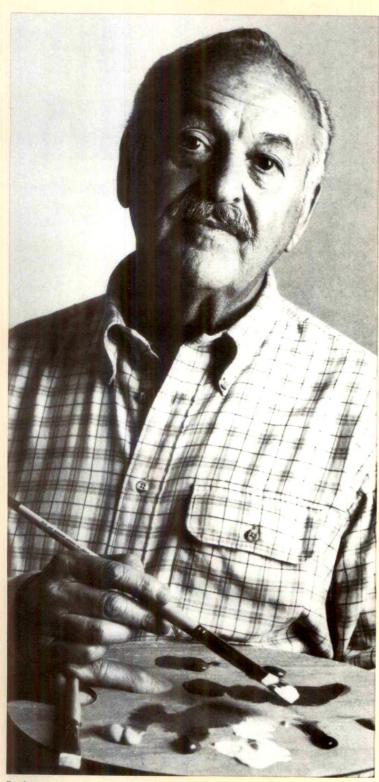
October 20–22, Third International Conference on Rural Rehabilitation Technologies, Grand Forks, N.D. Contact Deb Gasal, ICCRT Headquarters, Office of Clinical Development, Box 8202, University Station, Grand Forks, ND 58202; 701-780-2495.

October 21–22, annual meeting, Institute of Medicine, National Academy of Sciences, Washington, D.C. Contact Samuel O. Thier, M.D., President, 2101 Constitution Ave., N.W., Washington, DC 20418; 202-334-3300.

October 21–25, annual meeting, American Academy of Child Psychiatry, Washington, D.C. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-966-7300.

October 22–25, annual meeting, Academy of Psychosomatic Medicine, Las Vegas. Contact Sanford J. Hill, Executive Director, 70 West Hubbard St., Suite 202, Chicago, IL 60610; 312-644-2623.

# MOBAN achieved rapid control of severe symptomatology in just five days ...with only one 25-mg tablet day.



Professional model was used for this photograph. Case history on file at Du Pont Pharmaceuticals.

The efficacy and safety of MOBAN was recently demonstrated in a violent geriatric patient with delusional thinking and paranoid ideation. Taken to a hospital by force, the patient had assaulted his bedridden wife because he believed she was having an affair with a younger man.

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- Admitted as an involuntary patient, MOBAN succeeded in reducing his symptoms sufficiently to permit transfer to a psychogeriatric ward after just five days of treatment.
- Dosage was subsequently reduced to only 15 mg/day.
- After four weeks, there was no evidence of delusional thinking, paranoia or hallucinatory behavior.
- Even without anticholinergic medication, there were no side effects.

## Conclusion:

MOBAN was effective and safe at the low doses usually recommended for geriatrics who require major tranquilizers. Clinical experience with other geriatrics has also demonstrated efficacy with a rare incidence of significant hypotension, weight gain or impotence.

MOBAN is available exclusively from Du Pont. Please see following page for prescribing information.

Patient-friendly Psychiatric Products

**Du Pont Pharmaceuticals** 



## MOBAN® (molindone hydrochloride)

INDICATIONS: MOBAN is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of MOBAN was established in clinical studies which enrolled newly hospitalized and chronically hospitalized, acutely ill, schizophrenic patients as subjects.

CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause and in patients with known hypersensitivity to the drug

and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women, it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may supress or partially supress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic supression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy; Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause

allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially, advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient, calcium ions may interfere with the absorption of preparations containing phenyloin sodium and tetracyclines. MOBAN has an antiemetic effect in a quisals. A similar effect may occur in humans and may obscure sins of intestinal. effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of breast cancers are protectin dependent in Virto, a factor to potential mipotratice if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum profactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis, the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals:

Neurological—Extrapyramidal Heactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.
Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa). small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceeding paragraph under "Warpings."

Warnings:
Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used

Laboratory Tests: Rare reports of leucopenia and leucocytosis, treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, Buln, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant.

Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported infrequently, inclease in folious has been indeed in some patients, importance has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG.
Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100

Concentrate: 20 mg/ml in 4 oz (120 ml) bottles

MOBAN\* is a Registered U.S. Trademark of E.I. du Pont de Nemours & Co. (Inc.)

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State

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SR-1

JR-1

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FLEXIBILITY

## SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
   Tiltable Liquid Crystal Display
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- Audible warning prior to treatment
   Remote control capabilities
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- Built-in 2 channel digital chart recorder Numeric timing marks during monitoring
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SR-2

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# 39th Institute on H&CP American Psychiatric Association **Boston, Massachusetts Sheraton Boston** October 25-29. 1987

Please include me on the Institute's mailing list: Return to Susan Lash, Dept. H4, APA, 1400 K Street, N.W. Washington, D.C. 20005

Name	
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City	

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# For a Different Kind of Calm



Introducing
BuSpar
(buspirone HCl)

For Brief Summary, please see the last page of this advertisement

Mead Johnson Pharmaceuticals Introduces

# Buspirone HCl)

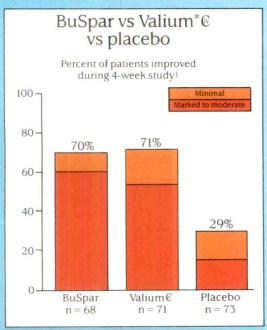
# A different kind of calm

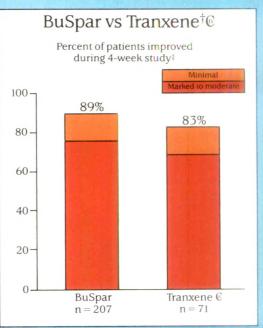
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.<sup>1,2,3</sup>

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy. 4-5

# Proven anxiolytic effectiveness over a 4-week course of therapy





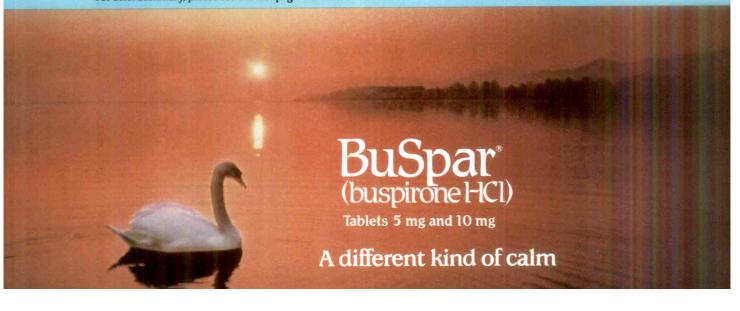
\*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.

‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,\* and cardiovascular and gastrointestinal complaints.

\*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.

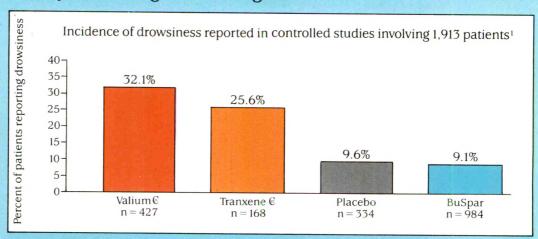


# Buspirone HCl)

# Anxiolytic efficacy without CNS-depressant activity

# Incidence of drowsiness no greater than placebo

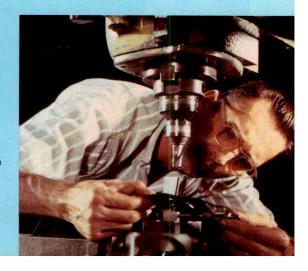
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.'



# No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.<sup>2</sup>

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.



# No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.\*3



# No apparent abuse liability

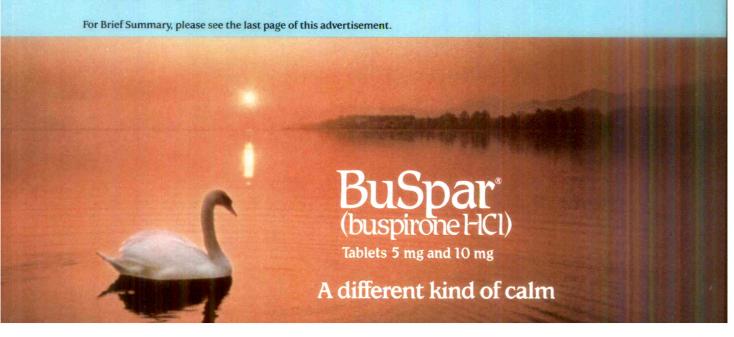
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.<sup>4.8</sup>

Well tolorated

# Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

\*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.



# Buspirone HCl)

# Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

# **Prescribing recommendations**

Initial dosage—5 mg t.i.d.

Week 1



**Dosage adjustment**—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

# At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is not a controlled substance.

# Patient selection

BuSpar will <u>not</u> block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a benzodiazepine to BuSpar:

- 1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
- 2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

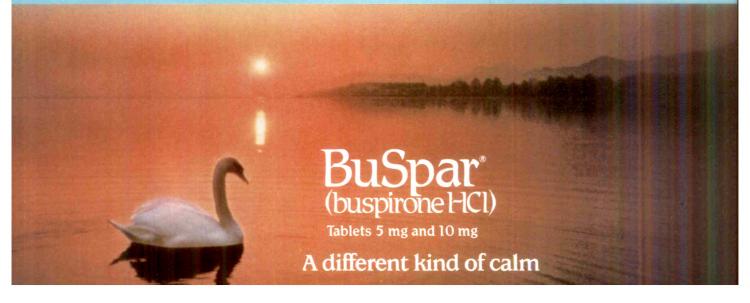
# BuSpar...the first choice in anxiolytic therapy when:

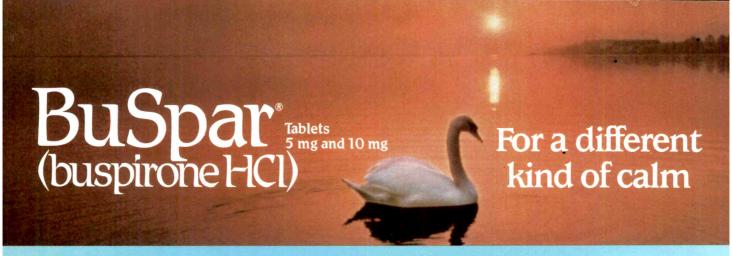
Treatment requires regular dosing for more than a few days

Patient functioning is key to safe and successful treatment

The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





## CONTRAINDICATIONS:

## WARNINGS:

The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

# PRECAUTIONS: General—

Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent

Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drugs use can be identified only after several years of marketing.

Information for Patients:

Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers: Administration to nursing women should be avoided if clinically possible

# Pediatric Use: The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly: No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, head-ache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:

The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily diszuziness, insomnia, nervousness, drowsiness, and light-header feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple com-

plaints, none of which could be characterized as primary.

## Incidence in Controlled Clinical Trials:

Incidence in Controlled Clinical Trials:

Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: Cardiovascular: tachycardia/palpitations 1%. CNS: dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. EENT: blurred vision 2%. Gastrointestinal: nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. Musculoskeletal: musculoskeletal aches/pains 1%. Neurological: numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. Skin: skin rash 1%. Miscellaneous: headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

## Other Events Observed During the Entire Pre-Marketing Evaluation:

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows. Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. Cardiovascular: Frequent was nonspecific chest pain; infrequent were syncope. hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. Central Nervous System: Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, suporo, and slurred speech and psychosis. EENT: Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were galactorrhea and thyroid abnormality Gastrointestinal: Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. Genitourinary: Infrequent were univary frequent, urinary hestancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. Musculoskeletal: Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. Neurological: Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. Respiratory: Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. Sexual Function: In

# DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

## OVERDOSAGE:

Signs and Symptoms:

No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

# Recommended Overdose Treatment: General symptomatic and supportive me

General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

## REFERENCES

- REFERENCES

  1. Newton RE, et al: A review of the side effect profile of buspirone. Amer J Med 1986;80(3B):17-21.

  2. Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. J Clin Psychiatry 1982;43 (12, Sec 2):45-55.

  3. Mattila MJ, et al: Acute effects of buspirone and alcohol on psychomotor skills. J Clin Psychiatry 1982;43 (12, Sec 2):56-80.

  4. Cole JO, et al: Assessment of the abuse liability of buspirone in recreational sedative users. J Clin Psychiatry 1982;43 (12, Sec 2):69-74.

  5. Rickels K, et al: Buspirone, clorazepate and withdrawal. American Psychiatric Association, 138th Annual Meeting, Dallas, TX, May 18-24, 1985. Abstract No. NR74, pg 51.

  6. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. J Clin Psychiatry 1982;43 (12, Sec 2):61-86.

  7. Con JB, et al: Dusble-blind comparison of buspirone and clorazepate in anxious outpatients. Amer J Med 1986;80 (3B):10-16.

  8. Griffith JD, et al: Investigation of the abuse liability of buspirone in alcohol-dependent patients. Amer J Med 1986;80 (3B):30-35.



**PHARMACEUTICALS** Bristol-Myers U.S. Pharmaceutical and Nutritional Group Evansville, Indiana 47721 U.S.A.

# Director Research Division

## Braceland Center For Medical Health And Aging

The Braceland Center for Mental Health and Aging, a partnership between The Institute of Living and The Travelers Center on Aging of the University of Connecticut Health Center, is seeking the Director of its Research Division. A Ph.D or M.D. Investigator with proven success in health policy and health services-related research in aging is sought. Leadership skills in bringing together investigators of different disciplines, including physicians, documented by a strong record of peer-reviewed publications, are essential. Evidence of prior success in competition for grant support of research projects, along with a national reputation in geriatrics and gerontology, should be available. Candidates should be eligible for senior (Associate or full Professor) academic appointment at the University of Connecticut Medical School.

Affirmative Action and Equal Opportunity characterize this search. Please submit CV and four letters of reference attesting to qualifications to Walter Kechich, M.D., Chairman, Search Committee. The Braceland Center for Mental Health and Aging.

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Experience The Rewards.



We are seeking candidates for head of the Psychiatry Department at The Mary Imogene Bassett Hospital. The appointment carries responsibility for providing leadership, teaching, and clinical care. The Department operates a 20-bed inpatient unit (voluntary, short stay), an active outpatient service including Child Psychiatry, and a Residency training program. The professional staff is made up of five Psychiatrists and three Clinical Psychologists.

Candidates should have substantial clinical experience as well as a successful academic and management background. We offer an attractive salary and fine benefits. The Mary Imogene Bassett Hospital is a regional referral and teaching center affiliated with Columbia University. The Medical Staff is organized as a salaried full-time group practice with a broad range of specialization. Our location in Cooperstown is a lakeside resort village with fine schools, outstanding recreational facilities, and a country lifestyle.

Please send c.v. or correspondence to:

John S. Davis, M.D. Chairman, Psychiatry Search Committee The Mary Imogene Bassett Hospital Atwell Road Cooperstown, NY 13326 (607) 547-3764



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Jointly sponsored by the New York State Office of Mental Health and Columbia University. Awardees will receive training in psychogeriatric issues. Opportunities also exist for graduate studies at Columbia's School of Public Health. Annual salary \$42,000-\$45,000. Based at Willard Psychiatric Center, located in New York State, with monthly assignments at Columbia in Manhattan. Candidates must have completed a four-year psychiatry residency and be eligible for licensing in New York. For information, contact Dr. John Toner, Center for Geriatries, 100 Haven Avenue, Tower 3-30F, New York, New York 10032, 212-781-0600.

# **TEXTBOOK** EFFICACY

# **FOR THE FUNCTIONING OUTPATIENT**

# Unsurpassed control of psychotic symptoms An unmatched record of clinical use With a highly favorable side effect profile

MELLARIL therapy is contraindicated in patients with hypertensive or hypotensive heart disease of extreme degree.



**TABLETS:** 10 mg, 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg thioridazine

CONCENTRATE: 30 mg/ml (each ml contains 30 mg thioridazine HCl, USP, and 3.0% alcohol, USP) and 100 mg/ml (each ml contains 100 mg thioridazine HCl, USP, and 4.2% alcohol)

MELLARIL-5" (thioridazine) SUSPENSION: 25 mg/5 ml (each 5 ml contains thioridazine, USP, equivalent to 25 mg thioridazine HCl, USP) and 100 mg/5 ml (each 5 ml contains thioridazine, USP, equivalent to 100 mg thioridazine HCl, USP)

FOR ORAL ADMINISTRATION

Caution: Federal law prohibits dispensing without prescription.

Before prescribing or administering, see Sandoz literature for full product information. The following is a

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree

Warnings: The risk of developing potentially irreversible tardive dyskinesia is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available of appropriate. There is no known treatment for tardive dyskinesia although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of tardive dyskinesia appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentialing central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atro-pine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During regnancy, administer only when the potential benefits exceed the possible risks to mother and fetus

**Precautions:** There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by dimi-nution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gyne-comastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsy-

chiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of tardive dyskinesia. **Adverse Reactions:** Central Nervous System—Drowsiness, especially with large doses, early in

treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness,

and pallor. Endocrine System — Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation and peripheral edema. Skin — Dermatitis and skin eruptions of the urticarial type, photosensitivity Cardiovascular System—ECG changes (see Cardiovascular Effects below). Other—Rare cases described as parotid swelling. It should be noted that efficacy, indications and untoward effects have varied with the different

phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. Cutaneous Reactions—Erythema,

Adultinitin Reactions—Missis, obstigation, a noticid, partylic least, cetaletest academic sectional eventual experiments and aplastic anemia, pancytopenia. Altergic Reactions—Fever, laryngeal edema, angioneurotic edema, asthma. Hepatotoxicity—Jaundice, biliary stasis. Cardiovascular Effects—Changes in the terminal portion of electrocardiogram including prolongation of 0-1 interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a biflid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between altered repolarization, not invocation damage, while there's indevidence of a class metalloriship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. Extrapyramidal Symptoms—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotenus, oculogyric crises, tremor, motor residessness, dystonic reactions, trismus, torticoms, opisitionius, occurging conses, trends, muscular rigidity, and akinesia. *Tardive Dyskinesia*—Characterized by involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long. term treatment. Since neuroleptics may mask the signs of tardive dyskinesia, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. Endocrine Disturbances—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, talse positive pregnancy tests. Urinary Disturbances—Retention, incontinence. Others—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome graded by progressive primentation of six or conjunctiva and/or appropriate by disciplination of the confusional states. marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythemalosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance,

and the smallest effective dosage should be determined for each patient. [MEL-Z37-5/1/85]



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# A Model for Ethical Problem Solving in Medicine, With Practical Applications

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Despite the dramatic increase over recent years in the research and teaching of medical ethics, there exists no theoretical framework within which to conceptualize ethical problems in medicine, to say nothing of solutions to these problems. The model proposed here attempts to fill this void by developing a conceptual understanding of the nature of moral dilemmas that can be applied to both theoretical and practical problems in medicine. Practical applications are demonstrated in three areas: personal ethical problem solving, hospital ethics committees, and the teaching of medical ethics. Suggestions are offered for the extension of these and other applications of the model, a model proposed as a foundation to be built upon through further research and daily experiences in a world of conflicting values.

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A difficult problem becomes a "dilemma" when we are quite sure that we will be making a big mistake regardless of whatever path we choose. It is instructive to consider moral dilemmas in this context. The anxiety we experience as we face each unpalatable alternative informs us about the nature of moral dilemmas. It seems that any decision we make will violate one or another value which we hold dear. Unfortunately, the many values that bear on any given dilemma are what philosophers call "incommensurable." That is, it is impossible to quantify just how much one value (say, social welfare or telling the truth) is "worth" in terms of another value (say, individual liberty or relief from suffering). Yet, as we choose

among possible actions, we are often forced to balance one incommensurable value against another, to balance a patient's individual liberty against social welfare, to balance our standards of truth-telling against the relief of suffering.

Perhaps the only scale we have to carry out such a balancing act is the anxiety that our conscience dutifully provides in the process. By striving to find the path that makes us least anxious, we presumably balance a host of incommensurable values according to the scale of our conscience: our anxiety increases as we contemplate trading off too much liberty in the name of social welfare or too much of the truth in the name of relieving suffering. This still leaves us feeling as if we have made a big mistake (since we have compromised values that we hold dear), but at least it is a good strategy for "cutting losses." We typically go through this process unconsciously, and it is quite difficult to articulate the pattern of balancing of values that we have achieved. It is, in fact, difficult just to list all of the relevant values that stand in need of balanc-

If we could articulate the various patterns of balanced values offered by our conscience, what we would have in their raw form are what we commonly refer to as our "moral principles." While we do not usually think of them in this way, our moral principles are the "equations" we claim to use when forced to measure incommensurable values against one another.

MORAL PRINCIPLES VERSUS MORAL ACTIONS: A PLACE FOR CONSISTENCY

The "balancing equations" that are our *moral principles* are generally much more complicated than the *moral actions* that we take as a result of the balancing—the unplugging of a respirator, the abortion, the psychiatric commitment. This distinction is important

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because doctors are typically concerned with where consistency fits into all of this—and it is no small matter that the demand for consistency applies at the level of principles, not actions.

This point is illustrated by the following true case of an obstetrician-gynecologist whose confusion about this issue led her to perform an abortion that she herself thought unethical. The doctor had always been a strong supporter of the abortion rights movement, and she firmly believed in "abortion on request" as a general principle. But in the case in question, an abortion had been requested only because modern technology, in ruling out various congenital abnormalities, had also determined that the fetus was female, and the mother decided she would rather have a boy. The doctor's own "instincts" (e.g., conscience) told her that this was not a good reason for an abortion. But, because she had always agreed to perform requested abortions in the past, she felt that "to be consistent," she would have to agree to do this one. She could not, however, seem to get the case out of her mind.

After further reflection, the doctor realized for the first time that her personal moral principle on abortion was much more complicated than could possibly be embodied in a universal action rule like "abortion on request." The case forced her to consider all of the values she held dear (autonomy of the mother, health and welfare of the mother and baby, social welfare, and so forth) that weighed on both sides of the abortion question. She then realized that she held the mother's autonomy and health as a preeminent value but not the only value—that in our modern world with its multiplicity of goods, ends, and values, no single value can have infinite and universally overriding weight. Her actual moral principle concerning abortion did indeed assign very great, but not infinite, weight to the mother's autonomy. The case was problematic for her because it was one in which that particular value was outweighed by others in the "balancing equation" that represented her moral principle. Only later did she come to understand that the demand for consistency applies at the level of principles, not actions. This was indeed one case where, to be consistent, she would not want to do an abortion when it was requested.

This case illustrates only the first step in this doctor's struggle to bring her articulated "moral principles" into harmony with her actual moral experience (i.e., the feelings engendered by her conscience as she considers each possible moral action). She is now armed with a new moral principle to guide her decision making, and her moral experience will be different, for having worked through this case, when she faces her next moral dilemma. Thus our moral experience and our moral principles are kept in an ever-evolving equilibrium as throughout our careers we have new moral experiences and reflect on our working moral principles. Early in this process it is easy to fall into the trap of believing that moral principles take a simple, universal form with the addition of a small number of

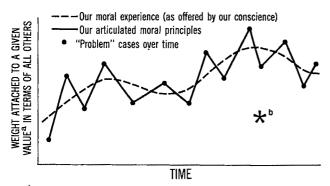
exceptions, such as "abortion on request except for sex selection" or "tell the whole truth unless the patient specifically requests otherwise." But with more experience the exceptions build, and the addenda "unless the patient requests otherwise, or unless a life will be endangered, or unless . . ." become recognized as the balancing of a set of values that come into play in diverse and seemingly unrelated ethical problems.

## A MODEL FOR ETHICAL PROBLEM SOLVING

The earlier conceptualization of how our moral principles and moral experience evolve has the advantage of reflecting our actual experience with the process. In teaching medical ethics to first- and second-year medical students over several years, I have been struck by the simplicity of medical students' early articulations of their principles ("never lie to a patient," "always do everything to save your patient's life") and by the evolution of their more mature principles as they struggle with the classic problem cases. When I was a second-year medical student, I once wrote an article defending the position of always telling patients the whole truth—a true testimony to the process I am now describing. (That article was, mercifully, rejected for publication.) Once I was in the clinical setting, it did not take long for my conscience to inform me of the problems with my simple principle, although my other early formulations still went something like: "tell the whole truth unless it will result in X, Y, or Z," as each successive problem case gave rise to another "exception." It was only later that I realized how many of these exceptions were the manifestations of other values competing with the value of truth-telling in my own value-balancing process. At that point it became possible to see how the megaequation of all the relevant basic values and their relative weights can become a practical tool for keeping moral experience and principles in their dynamic equilibrium: each new dilemma exposes a novel division of values conflicting around the facts of a case and thus sharpens our own weighting system as we reflect on the problems associated with each alternative action.

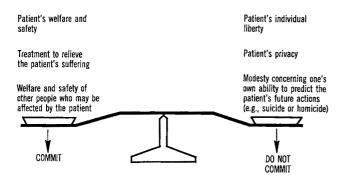
This is a variation of John Rawls's notion (1) of a "reflective equilibrium." As shown in figure 1, each new moral dilemma we face helps us clarify our moral principles as we reflect on the conflict between basic incommensurable values weighing on each side of a case. Armed with our new understanding of the principles on which we plan to base our future decisions, we find that our moral experience is also different when we face the next problem case. Obviously, these problem cases or dilemmas are more than simply nasty situations: they also present a new opportunity to learn about our principles and realign them with our moral experience. (It is often difficult to appreciate this opportunity in the heat of the moment, and it is usually in later reflection that equilibrium is restored—hence a "reflective" equilibrium!)

FIGURE 1. Change Over Time in Relative Weight We Attach to a Given Value as Reflected in Our Moral Experience and Articulated Moral Principles



<sup>a</sup>Such as individual liberty, telling the truth, or relief from suffering. <sup>b</sup>The asterisk demonstrates how the model may be used to minimize "countertransference distortions," as described in the text discussions of practical applications.

FIGURE 2. Model of Conflicting Values in the Ethical Problem of Psychiatric Commitment



A good way to carry out this process is by actually writing lists of the conflicting values in each case. An example of a basic list for the ethical problem of psychiatric commitment is shown in figure 2. This is typical of an initial list one might devise when approaching a commitment case for the first time. With added experience, many more values are identified as weighing on each side of the scale. The best vehicle for developing one's own moral understanding comes from saving these lists and watching how they develop over time. By observing the evolution of these lists of values in conflict, it becomes possible to watch one's own "figure 1" develop around a given ethical dilemma.

## WHAT IS MEANT BY "MEDICAL ETHICS"?

By following the evolution of lists of values such as those described earlier, it also becomes possible to understand how the expression "medical ethics" can have real meaning. At first, this common expression may not appear to be at risk for lacking substantive meaning, but the weight of hundreds of years of moral

philosophy is against it. If Immanuel Kant (2) left any legacy of thought at all, it is our modern notion that "moral rules" must by definition apply to every person equally. For the past decade, Americans have been quick to remember this when a suggestion is made that "Presidential ethics" can refer to something other than the ethics that apply to all of the rest of us. Thus, the notion of a separate field of "Congressmen's ethics" would immediately raise the question of meaning in a way that medical ethics seem not to do.

One simplistic solution is that, since doctors are engaged in making certain types of decisions that others are not, medical ethics refers to the field of ethical issues that tend to be faced by doctors because of the work they do. This conceptualization is coherent, but it lacks depth, especially as increasing numbers of nonmedical professionals find themselves entwined in these same ethical issues. A second simplistic solution would be to try to abolish the expression "medical ethics," reminding people of the dangers that lurk if doctors (or politicians) start to think that they have a different code of ethics from everyone else just because of their role in society. This solution is neither practical nor desirable, given that there is a third and useful way to conceptualize the problem of medical ethics.

The third solution focuses on the pattern that develops as doctors struggle with lists of values and their relative weights around the many ethical problems they face each day. By studying such lists across diverse moral dilemmas, it becomes possible to uncover a pattern of value balancing that is characteristic of medicine as an institution and that distinguishes medicine from other professions. Dedicated as it is to the relief and prevention of suffering, medicine is anything but value-neutral from the start. It is therefore not surprising that medicine gives relatively more weight to considerations of welfare than to considerations of justice as compared to the legal profession, for example. In law, the crucial factor in what to do now is often that of justice, which forces lawyers to painstakingly assess how people got into their current predicament. In medicine, the backward-looking issues of justice and guilt weigh less heavily than in law. In allocating resources to two patients with liver disease, doctors consider the patients' welfare (i.e., the consequences for the patients' health) much more than they consider whether or not one patient is more to blame for his or her condition (for example, when one case was caused by excessive ingestion of alcohol, while the other came from inadvertently eating the wrong clam). Medicine as a profession thus manifests a certain pattern of value balancing that distinguishes it from the legal profession. The suggestion here is that the pattern of value balancing that is characteristic of medicine (e.g., assigning relatively less weight to justice than to welfare as compared to the legal profession) is what gives meaning to the expression "medical ethics," which refers to this medical pattern.

How this pattern came to be and how it is perpetuated are no small matters. Obviously, a two-way street

exists, wherein young people choose medicine as a profession because they have been raised with and already hold this pattern of values while, at the same time, the established profession, through medical education, teaches this pattern to medical students and house staff, who become "socialized" into the profession, or "professionalized" (to friends of the process). Given these strong forces at work, it is not surprising that attempts to force radical changes on the values of medicine are likely to fail. Those who would like to use insurance ploys to force doctors to treat differently those two patients with liver disease underestimate the power of medical ethics. Some insurers may wish to charge higher premiums to smokers or obese people, but they should not be surprised if doctors refuse to give less care to smokers than to nonsmokers when treating their cancers.

## ADDED LEVELS OF COMPLEXITY

Before we move to applications of the model described earlier, a number of added levels of complexity should at least be mentioned. For example, a distinction is often made in moral philosophy between what J.L. Mackie (3) has called "morality in the broad sense" and "morality in the narrow sense," Morality in the broad sense refers to the search for general action-guiding principles. As we consider the moral thing to do (in the broad sense), we might weigh aesthetic considerations, the demands of etiquette, our own selfish wishes, and so forth. In addition to these, we would also weigh what is often called the issue of "morality," taken now in the narrow sense. Morality in this narrow sense refers to only those considerations which are founded on basic values and which seem to operate through our consciences to counteract some natural tendency we might otherwise have to be selfish (4). It thus makes sense to say "I know morality dictates X, but there are other considerations here," only when speaking of morality in the narrow, not the broad, sense. Both of these senses of morality are commonly used (and often confused), and we all too often achieve some understanding of one only to apply that understanding inappropriately to the other.

What I have written earlier applies to morality in the narrow sense. It is possible to use the same framework to model medical morality in the broad sense, but it is much more complex. In addition to the basic value-balancing act we face with a given moral dilemma, we are also operating within a web of institutions (our culture, state and federal law, a hospital), each of which has a somewhat different characteristic pattern of balancing values. It is the conflict among these different patterns that gives rise to the deepest of conflicts of interest in medicine. Thus, in the commitment example in figure 2, it may be fine to decide that a patient's individual liberty outweighs his or her need for treatment in a given case, but if the patient is mentally ill and at all homicidal, the law requires that

he or she be committed. (The law assigns relatively more weight than does medicine to the consideration of individuals other than the one in question.) Similarly, the current debate over for-profit hospital corporations focuses on the effects that must inevitably result when doctors choose to operate within yet another institution with yet another pattern of value balancing which differs from that of the institution of medicine (5).

Examples in which doctors are forced to act as "double agents" (as when psychiatrists [6] are called on by society to protect society from dangerous mentally ill people and not just serve their patients) highlight the difference between morality in the narrow and the broad senses, but these added levels of complexity are always operating, since decisions are always being made within a web of institutions. It would be possible to add "obedience to the law" to the values in figure 2, but it would have to be placed on both sides of the scale, since it might weigh in either direction depending on the facts of the case.

In fact, legal considerations are not the only ones to weigh on both sides of the scale, and this represents another added level of complexity. It is not uncommon for a value, such as personal autonomy, to weigh on both sides of a case—especially when this value arises with regard to two different individuals. But the same value may appear on both sides of the scale even with regard to the same person, as when there are quality of life issues weighing on both sides of a case concerning artificial life support. In these cases, it becomes useful to examine how these values come to appear on both sides and in what context they do so. As will be seen later, it is the working through of such problems that usually makes the best decision clear.

Finally, as one more added level of complexity, it is worth noting that if medical ethics is meaningful as a characteristic pattern of balancing values, this may differ from the pattern that represents the personal moral principles of an individual physician. It is one thing to observe the "two-way street" of medicine inculcating medical values in young doctors and young people choosing medicine because they hold those values already, but it is another to pretend that personal codes of ethics on the part of even the most well-intentioned physicians will always coincide with those of the profession as an institution. This is particularly a problem for young doctors who have not yet had enough experience to internalize many of the values of the profession. When such conflicts arise in medical students and house staff between, as one fourth-year medical student once put it, "what I feel I should do as a doctor and what I feel I should do as a person," it is important not to underestimate the power of that experience in the process of professionalization. Within medicine's characteristic pattern of balancing values, there is great scope for differences of opinion between intelligent and "ethical" doctors. This is indeed what makes medical ethics such an important (and lively) field for discussion and research.

# APPLICATIONS TO PERSONAL ETHICAL PROBLEM SOLVING

When we apply the model of ethical problem solving to the ethical dilemmas we face daily as physicians, the most striking quality that stands out is just how personal the process is. It is not surprising that once physicians start writing out their lists of competing values over time, they keep those lists under lock and key. The personal nature of our moral principles is hardly surprising, since these principles reveal parts of us that we often hide from ourselves, let alone from friends or colleagues. (Even in the confidence of psychoanalysis, it is often only through analyzing our resistance to facing such matters that the analyst comes to understand them!)

This emotional side of what might otherwise be considered a rigorous intellectual procedure for solving ethical problems should warn against a dangerous trap—that of using the procedure to lie to ourselves. Consider, for example, the case of a terminally ill patient in great pain from the bony metastases of her cancer, who seems unable to be weaned from her respirator. We set out to use our conscience to balance the values involved by anticipating the anxiety we feel as we contemplate our various alternatives. But maybe what we are really doing as we choose to "pull the plug" is not carrying on our reflective equilibrium at all: perhaps it is merely processing the anxiety we are feeling because our own mother or grandmother is (or was) in a similar situation in which we felt powerless to change things. This is the factor that might be called "countertransference distortion" (by analogy with the distortion arising from the analyst's own unconscious issues in a psychoanalysis). It is a factor that is difficult to separate from the process described earlier, but one that must be considered in every case. Our personal experiences outside our professional lives must and should influence our moral experiences within our professional lives. We must, however, be on guard for "outlying points on the curve," like the asterisk in figure 1. Notice that, as drawn, the asterisk would have been less of an outlier earlier in time, however. Indeed, it is only by having a fairly good idea of where our equilibrium is and has been (i.e., by being the "well-analyzed analysts of our dilemmas") that we can prevent ourselves from letting such personal issues interfere with our professional moral integrity—one of the most difficult challenges of all.

When we have made the effort to work through this difficult balancing act, the personal rewards are equally great. We can, for one thing, defend our decisions against the criticism of others, as well as against our own self-doubt. A doctor may be criticized (or criticize himself or herself) for having failed to give enough weight to a patient's individual liberty when the patient is committed into a hospital, for example. The accusation is made: "Well, I guess that person's individual liberty did not mean much to you" (or "to me" in the case of self-doubts). Having worked

through the difficult balancing of values, however, we know that the patient's liberty meant quite a bit to us—it was, in fact, the value we attached to the patient's liberty that made the decision so difficult. Once such trade-offs are understood within the context of the model, then, it is of the utmost importance to remember that the values which are outweighed in a given case were far from "nothing" to us. The pains we take in making decisions in the face of dilemmas testify to the priority that we did indeed attach to those values which were ultimately outweighed. It is in this way that we can understand what is meant when we say that we give honor to life not by always preserving life at any cost but by the pains we take when we make decisions that have the opposite effect.

## APPLICATIONS TO HOSPITAL ETHICS COMMITTEES

Many institutions, particularly hospitals, have recently developed standing ethics committees that serve functions varying from support group, to educator, to tribunal. Some of these committees merely form a forum for discussion, while others hand down actual (binding or nonbinding) recommendations for action (7). Since many of the most difficult ethical problems within an institution are now addressed by a committee, it is worth mentioning how the model described earlier might be used (or abused) in such a setting.

Each member of an ethics committee brings to it a great variety of experience with balancing values one against another in a great variety of contexts and within a great variety of institutions. A certain amount of self-selection usually occurs, and members of the committee typically have relatively strong, well-articulated moral principles. They may not put it in these words, but they each know pretty well how much safety they are willing to trade off for how much privacy, how much welfare for how much justice. The ethics committee itself, however, forms a new and unique institution that tends to polarize its members: the member who gives the most weight to justice considerations (relative to other values)—even if only marginally so—will quickly become the group's "defender of justice" (this member will often be a lawyer if there is one on the committee, for reasons discussed earlier). As case after case is addressed by the committee, members soon come almost to expect the "defender of privacy," the "defender of social welfare," and the "defender of patient autonomy" each to take his or her ground. Indeed, the knowledge that the defenders of patient autonomy and privacy are at the committee meeting makes it easier for the defender of social welfare, for example, to argue for the involuntary commitment of an arguably dangerous mentally ill patient. After all, the balancing of many other values against social welfare no longer has to be carried out in the mind of any given member; it instead gets carried out among members, each of whom argues for the weight of one or two values only.

The group dynamic I am now describing is, of course, one of the most basic of group behaviors. A form of group projective identification, it is the process by which conflicts really occurring in the mind of each group member get played out within the group, as each member accepts and "holds for the group" one part of the story. In observing this process as a member of a medical-school-affiliated community hospital ethics committee, I have been impressed by how vividly the committee as a group can demonstrate the model that I have proposed for individual ethical problem solving. This is not merely an interesting group dynamic; it has important practical correlates as well. Ethics committees are often charged with making policy recommendations to the hospital's governing body (or actually setting policy in some cases, either through precedent or more formally). In choosing among a wide spectrum of policy options, an ethics committee can use to great advantage the process by which competing values become represented by different members, as the following example will demonstrate.

Our ethics committee was asked to consider the case of a nurse who had accidentally stuck her finger with a needle that had been used to draw blood from a homosexual patient suffering from pneumocystis pneumonia. The patient had a presumptive diagnosis of acquired immune deficiency syndrome (AIDS), although he refused laboratory testing for both T-cell subset ratios and human T-cell lymphotrophic virus type III (HTLV-III) antibody titers. He stated that he had no desire to know the results of such tests himself and feared that the information would be used against him, if not in the hospital, then by potential employers who might ask about such tests should he, at least temporarily, be back in the job market. The nurse said she wanted to know the patient's HTLV-III immune status, even though she claimed to know all the data on needle stick "exposures" to AIDS and problems with HTLV-III antibody testing. She said she realized it was not like a needle stick exposure to hepatitis, in which the hepatitis immune status of the patient might lead to prophylaxis for the nurse, since her behavior in this case would be unaffected by the result of the test. (She stated that she planned to have her own HTLV-III antibody titer checked every 6 months.) She did, however, believe that she had a right to the information, and she based her claim partly on her having sustained the needle stick in the course of caring for the patient.

A deadlock ensued when the patient repeatedly refused to give consent for the tests, and the case was brought before the ethics committee. As the committee members took up their "established positions" (the "defender of privacy" speaking for the patient's fears of discrimination, and so forth), a number of constructive new policy options were articulated as the members sought specific ways of preserving the values that seemed to conflict. If the patient's decision to refuse the test was really based only on his fear that the information would get into the wrong hands (or even if he

himself also wanted not to know), perhaps the pathology department could devise a triple-blind coding system so that only the patient and nurse (or even only the nurse) could ever find out the result. The value of privacy could then be upheld without having to trade off anything else. If the patient still refused, his autonomy stood in direct conflict with the nurse's wishes, and privacy was not the issue. Other supports could then be put in place for the nurse, including further education about such tests and their meaning, to give what reassurance she sought without having to compromise the patient's right to refuse the tests (which the committee felt must outweigh the nurse's desire to know the result). And so what was in the beginning a question of "should we do the test or not" turned into a discussion of the numerous actions that might maximize all of the values that seemed to conflict, before any trade-offs must, in the end, be made.

The policies developed by an ethics committee are the analogue of an individual's moral principles. The policies define the "balancing equations" that calculate how much of one value is to be traded off for others when such trade-offs must be made. We see in the development of such policies the same equilibrium discussed earlier: people's moral experiences, offered by their consciences, affect the policies developed; but the policies, once photocopied and hung around the hospital, will also affect people's moral experiences when the next problem case arises. Since their policies affect the moral experience of the entire hospital community, ethics committees must take extra care in deciding when, how, and whether or not to establish any given policy. Even a well-written and thoughtful policy, if poorly timed, can disrupt the moral environment of an institution strained by values in conflict. (It is easier to discuss how the professions of medicine and law might differ in their characteristic pattern of balancing values than to note the obvious fact that nursing, social work, hospital administration, and other related professions each also have their own pattern of balancing values which differs from that of medicine—a fact that we often find embarrassing and try to ignore.)

The main point here, however, is that an ethics committee can use the process by which it balances values among members to create new policies that alleviate the need for trading off one value for another, and the same outcome can and should be achieved by individuals balancing values within their own conscience. Once the values in conflict are understood, the original dilemma-stated as an unpalatable choice between "tell the whole truth or lie" or "commit the patient or just let him go"-may dissolve through the many options that might preserve the truth and relieve suffering, respect the patient's liberty and preserve social welfare. This, after all, is the most desirable outcome when we are faced with a dilemma: not to have to choose after all between the "big mistakes" in question.

## APPLICATIONS TO TEACHING MEDICAL ETHICS

I shall conclude by discussing the proposed model with regard to the teaching of medical ethics in medical schools and residency training programs. I do not mean to discuss here the practical side of how a given group of students might apply the model to learn about various specific moral issues (which could be done in a variety of ways). What I would like to address is, in essence, the relationship between theory and practice.

The dynamic equilibrium represented in figure 1 is, in a way, an equilibrium between theory and practice, between one's intellectual understanding of one's moral position and one's actual moral experience. It may well be that the curve will end up in the same place eventually whether the first step in the equilibrium comes from the theory or the practice side, but early on the difference may well be dramatic. If, for example, one's first struggle to articulate personal principles about abortion occurs after, as a third-year medical student, one has assisted with a second-trimester abortion, the practical, experience side will likely set the equilibrium in a definite direction. (This is why the antiabortion movement uses grotesque photographs to "educate" people to consider the pros and cons of abortion.) If, instead of the practice side, the theory side started off the process—if as first- or second-year students the individuals in question were forced to balance the values involved for themselves their moral experience in the operating room would likely be somewhat different, and the equilibrium would be set in motion initially in a somewhat different direction.

The relationship between theory and practice, and which comes first in medical training, is thus no small matter. Of course, theory cannot exist in complete isolation from practice, and so cases must be used to focus the theory even in preclinical ethics courses. But this effort pays off when the students, in their clinical training, come to new moral experiences with more mature moral principles. In medical training we do not wait until people's lives are at stake to teach anatomy and physiology. Neither should we wait until moral choices must be made to teach medical ethics. Ethics must be taught alongside every clinical decision, but solid foundations must be laid for moral as well as clinical decision making.

For the past 5 years I have been teaching medical ethics to first- and second-year medical students at Harvard Medical School. My belief that the equilibrium should start with theory goes beyond the preclinical stage of training of the students in the classroom. The course itself begins by introducing the values themselves—what is meant by welfare, justice, liberty, and so forth. If these concepts become the tools that are used to dissect ethical problems, surely they should be analyzed before their *meaning* might be prejudiced by weighing one against the next in a medical context. Indeed, to resist the effects of the class's prejudices, the

values in question are introduced through a historical review of their development and of the various moral theories through the ages that emphasized the primacy of each. Only then are the classically problematic moral issues in medicine addressed, week by week, by students prepared to methodically balance the many values that conflict around each case.

This application to the teaching of medical ethics thus enables each future doctor to sharpen his or her own moral position by using a rigorous problem solving method. By focusing each student's attention on his or her own moral experience, the model I have described provides a tool for thinking about ethical problems—a tool that teaches how to think, not what to think. Teaching medical students what to think about ethical issues has no place in medical education in a free society—it is merely propagandizing of the worst kind. As a tool for conceptualizing ethical problem solving, the model I have discussed enables teachers to teach the proper subject of the medical ethics curriculum: how, not what to think.

Each of us can use the model to come to our own conclusions about how to act in any given case. By focusing our attention on the particular values in conflict, we sharpen our own moral position and evolve in the reflective equilibrium that exists between our moral principles and our moral experience. But the model does a bit more than that. It also provides a context within which we can carry out meaningful and productive moral argument. Just as I challenge my students to define their own pattern of how each value is to be weighed against all others, we must all continually challenge one another to do the same as the process of moral education continues through our lives. Only then can we understand how different points of view really conflict, and only then can we each preserve the vitality of our own morality.

## SUMMARY AND CONCLUSIONS

In this article I have introduced a model for ethical problem solving in medicine and discussed a few of its practical applications. It is a descriptive model in that it seeks to demonstrate certain basic principles by modeling the behavior we see around us every day. In particular, the model focuses on the conflicting values that give rise to the "dilemma" nature of ethical problems. Moral principles are conceptualized as the "equations" offered by our conscience that compute how much each value is "worth" in terms of each of the other conflicting values, and these principles are found to evolve in a dynamic "reflective equilibrium" with our moral experiences. The moral actions we take are determined by the ultimate balance of relative weights assigned to all of the competing values as they arise from the particular facts of a problematic case and so each new dilemma helps us develop our principles by introducing new patterns of conflicting values. The effort it takes to carry out such a balancing act

in a problematic case reminds us that the outweighed values were not "nothing" to us in that process, and this itself can help avoid many misunderstandings and confusions.

The model dismisses the simple-minded position of those who define their moral principles in terms of adherence to a consistent action (always tell the whole truth, always preserve life at all costs) by emphasizing that consistency applies at the level of principles, not actions. If one's principle incorporates a given tradeoff among the preservation of life, individual autonomy, and relief from suffering, different cases are bound to result in different actions, but consistency is still found at the deeper and appropriate level. Medicine itself is not neutral with respect to trade-offs between values, and the pattern of value balancing characteristic of medicine as a profession gives rise to what is commonly called "medical ethics"—an ethics that may conflict with that of other institutions within which doctors must make moral decisions (and may at times conflict even with doctors' personal codes of ethics, particularly at early stages of their training).

The practical application of the model to ethical problem solving reveals a number of advantages, not the least of which is the possibility of finding alternative solutions that avoid the "dilemma position" altogether. By considering the actual values that are in conflict, we may discover options that alleviate the need to trade one off against another—the best of all possible solutions when it can be achieved. Keeping track of our own reflective equilibrium thus not only prevents our stated moral principles from straying too far from our moral experiences, it presents a strategy for maximizing adherence to all of the values that we hold dear. It also enables us to defend our moral position against criticism, to identify where points of real conflict exist with others and thus make moral discourse more meaningful, and, crucially, it can enable us to see when personal (countertransference) issues are giving rise to feelings that lie far off the curve of our reflective equilibrium. Writing successive lists of values on pieces of paper over time may seem like a

simple-minded exercise, but it is one of the only ways to avoid the dangerous trap of lying to ourselves about our own moral position when difficult personal issues confuse our rational approach to ethical problem solving.

My introduction of a few practical applications of the model (to hospital ethics committees, medical ethics teaching, and personal ethical problem solving) is intended only as a beginning. A great number of applications can be made. For example, cross-cultural ethical problems can be understood by recognizing that different lists of values are in conflict, rather than merely different weightings of the same lists (as is usually assumed but is true only in single-culture problems). Health policy issues might be analyzed in terms of the competition within the political arena of each relevant institution's characteristic pattern of value balancing. And so on. My goal here has simply been to introduce a method of conceptualizing ethical problem solving in medicine. The examples are meant primarily to define the model better and show how it might be put to work. Just as theory and practice sharpen one another in an evolving equilibrium within the model, so too will the model itself evolve as it is applied in different contexts by different people. This is how deeper understanding develops, both within the medical community and within each of us.

## **REFERENCES**

- Rawls J: A Theory of Justice. Cambridge, Harvard University Press, 1971, pp 48–51
- Kant I: Critique of Practical Reason (1788). Translated by Beck LW. Chicago, University of Chicago Press, 1949
- Mackie JL: Ethics: Inventing Right and Wrong. Baltimore, Penguin Books, 1977, pp 106–107
- 4. Warnock GJ: The Object of Morality. London, Methuen, 1971
- Relman AS: The new medical-industrial complex. N Engl J Med 1980; 303:963–970
- O'Brien Steinfels M, Levine C (eds): In the Service of the State: The Psychiatrist as Double Agent. Hastings-on-Hudson, NY, Hastings Center, 1978
- Fost N, Cranford RE: Hospital ethics committees. JAMA 1985; 253:2687–2692

## The Legal Basis of Forensic Psychiatry: Statutorily Mandated Psychiatric Diagnoses

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Using the Oregon statutory scheme as an example, the authors review certain areas of the law where psychiatric expertise is mandated by statute. This review points out the diversity of determinations where forensic psychiatric expertise is required by law. The authors' thesis is that forensic psychiatry draws its vitality from the law. Legal requirements, however, should not dictate psychiatric response, which should be guided by psychiatric knowledge and ethical concerns.

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Porensic psychiatry is a controversial subspecialty of psychiatry. The controversy became even more intense and visible after the 1982 insanity verdict in the case of John Hinckley, Jr. In a public opinion survey conducted in Delaware 1 week after the Hinckley verdict, Slater and Hans (1) demonstrated that the public had little confidence in the psychiatric testimony offered at the trial and little faith in the forensic psychiatrist's ability to make meaningful determinations of legal insanity. Negative views of forensic psychiatry are not confined to public opinion. The psychiatric profession itself is actively debating the role of forensic psychiatry and its effects on the profession as a whole.

In a 1984 discussion of the destigmatization of mental illness (2), John Talbott, then President-Elect of APA, commented on forensic psychiatry:

As a coda, let me suggest that our inability to look anything but ridiculous in the celebrated courtroom battles of the experts over the existence of mental illness or lack of it in criminal suspects makes the process of destigmatization of our patients all the more difficult. This Association must find some way to protect the seriously ill from being punished for acts they committed when incomprehensibly psychotic, while eliminating the spectacles that occur all too frequently between our so-called forensic experts and that tarnish all of us and our patients.

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These familiar criticisms focus on practical problems ostensibly created for psychiatry by the participation of forensic psychiatrists in adversarial legal proceedings. Other commentators, such as Stone (3), have questioned the ethics of forensic psychiatry. Attempting to find a middle ground within the psychiatric profession while making a strong and positive appeal to public opinion, APA published a 1983 position paper on the insanity defense itself that attempted to define some roles for forensic psychiatrists within the criminal justice system (4).

Facing heavy attack from within the psychiatric profession as well as outside, where does forensic psychiatry draw its strength and how does it retain its vitality? In this paper we contend that the strength of the field comes from the law itself. Forensic expertise is statutorily mandated. In many areas of the law there is a defined need to know about the mental condition of persons involved in the proceedings. Psychiatric diagnoses are prerequisites for many critical determinations in the civil law and criminal justice process. In this paper we will focus on areas where psychiatric diagnosis is required by law. We will also examine the pervasive need in statutory law for the determination of dangerousness.

We hope to demonstrate that forensic psychiatry has a solid foundation in statutory law and, further, that the law takes a utilitarian approach to psychiatric diagnosis and chooses what it wants to hear from psychiatry, often in seemingly inconsistent ways in different contexts. Finally, having demonstrated what the law wants from psychiatry, we will discuss some of psychiatry's past responses and current options. The fact that statutes call for psychiatric diagnoses and determinations of dangerousness does not mean that psychiatrists must come forward to make these determinations. Psychiatry's options in this regard will be discussed in the light of the options available to those who practice forensic psychiatry in the face of increasing criticism and hostility (5).

We will focus on psychiatric diagnosis and the determination of dangerousness as required by certain civil and criminal statutes. To illustrate, we will use the Oregon statutory scheme as a model to highlight areas of the law where psychiatric diagnoses are required. Similar, if not identical, schemata can be constructed for other state and federal jurisdictions. We chose Oregon because of our familiarity with its statutes.

We examined Oregon's laws and identified all statutes calling for a psychiatric diagnosis or for a "near diagnosis." Each requirement for psychiatric opinion will be noted, with particular attention to areas of controversy.

#### **CIVIL STATUTES**

#### Civil Commitment

For the purposes of civil commitment, Oregon defines a "mentally ill person" as a "person who, because of a mental disorder is either: (a) Dangerous to himself or others; or (b) unable to provide for his basic personal needs and is not receiving such care as is necessary for his health and safety" (6, 426.005).

Two controversial areas appear in this definition: the lack of definition of the term "mental disorder" and the determination of dangerousness to self or others. We believe that the legislature did not define "mental disorder" and that case law has kept the definition very broad for the specific public purpose of attempting to provide a place for the detention, evaluation, and treatment of potentially dangerous persons. In fact, in 1984 the Oregon Court of Appeals ruled that alcoholism is a mental disorder for purposes of civil commitment (7). This leaves the psychiatrists, other mental health professionals, and judges involved in this process with wide latitude in relation to psychiatric diagnosis. Even though the definition of the term mental disorder is broad, the law clearly expects that the judge will base decisions on expert opinion and testimony.

One area of controversy is whether the test for civil commitment, even with its broad concept of mental disorder, is applied too narrowly, allowing persons with personality disorders who might potentially be dangerous to remain in the community. Research into civil commitment in Oregon (8) suggests that individuals with personality disorders enter the system but that few go all the way through the process to commitment. In examining the Oregon commitment process, Shore et al. (9) found that 16% of 189 persons entering the civil commitment process were diagnosed as suffering from personality disorders. Only 2% of this group of persons with personality disorders were eventually committed.

Nonetheless, it can be argued that even the abbreviated process augments public security to some degree, because those crisis-prone individuals who have personality disorders and who might be occasionally dangerous can be detained on an emergency basis by police and physicians for up to 5 days before their court hearing. In many cases this brief period allows for some degree of crisis resolution and short-term treatment.

It is thus not surprising that mental disorder, as it appears in Oregon's civil commitment statute, is retained as a broad category so as not to restrict its

availability as a potential means of avoiding harm to persons. Dangerousness is thus the central issue in this area; the diagnosis serves as an entry point to the more important legal concern. This view of diagnosis and dangerousness carries through most of the determinations discussed in this paper.

#### Sexually Dangerous Persons

This statute provides for the civil commitment of persons defined as sexually dangerous. In recent years in Oregon the statute has been used with decreasing frequency in favor of criminal prosecution of sex offenders, followed by the possibility of treatment in a program run jointly by the corrections and mental health systems once the offender has been sentenced. As defined by statute, a "sexually dangerous person" is "a person who because of repeated or compulsive acts of misconduct in sexual matters, or because of a mental disease or defect, is deemed likely to continue to perform such acts and be a danger to other persons" (6, 126.510).

As in civil commitment, the diagnosis called for is not clear but combines the concepts of repeated and compulsive acts of sexual misconduct with mental disorder and dangerousness, which is again central to the determination. Perhaps this test could be applied without forensic psychiatric testimony; however, the inclusion of the term "mental disease or defect," even in the alternative, ensures that experts will be consulted in this area.

#### Guardianship

In order to have a guardian appointed in Oregon, a person must be an "incapacitated person," defined very generally as "a person who is unable, without assistance, to properly manage or take care of himself or his personal affairs" (6, 126.003). Although not specifically calling for psychiatric diagnosis, the statute is broad enough to allow psychiatric testimony in guardianship proceedings. Lawyers and judges are often eager to look to mental health experts for guidance in such decisions. The test has been applied only occasionally in Oregon to appoint guardians for mentally ill persons (10).

#### Other Civil Tests

Lawyers use the testimony of psychiatrists in many other areas of the civil law, such as determinations for workers' compensation, personal injury, testamentary capacity, and child custody. However, these areas stand in contrast to the statutorily mandated diagnoses that are the theme of the present paper. A brief discussion of workers' compensation will illustrate the difference.

Oregon's workers' compensation statutes do not contain any reference to mental disease or defect. There is no statutory test that requires a psychiatric diagnosis per se. However, the statute does provide that any occupational disease is compensable. Over the years, Oregon courts, like courts in most states, have decided individual cases in which they allowed compensation for mental diseases. That is to say, the courts have gradually broadened the definition of "disease" to include mental diseases as well as more traditionally compensable physical diseases.

Accordingly, lawyers have increasingly turned to psychiatrists to diagnose and testify about mental diseases claimed to be related to job stress. But they are not required to use psychiatric testimony to make their case. Furthermore, most workers' compensation cases do not involve mental diseases, and there is therefore no participation by psychiatrists. Personal injury cases illustrate the difference even more starkly. The statutes themselves contain no reference to disease of any sort. Psychiatrists are often called into court but not because of any statutory test.

This is in contrast to the other legal areas discussed in this paper, which include a statutory test that effectively mandates psychiatric testimony. Thus, for example, civil commitment cases always involve participation by mental health experts because the statute requires a statement that the subject has a "mental disorder." Both categories of cases are important to forensic psychiatrists. But we concentrate in this paper on those areas of the law with statutorily mandated diagnoses because we believe they are at the core of forensic psychiatry and because they are the areas that have generated the most attention.

#### **CRIMINAL STATUTES**

#### Competency to Stand Trial

This is a critical determination in the criminal law and an area that has had its own share of controversy. Determinations of competency to stand trial are not particularly concerned with the issue of dangerousness. The main issue here relates to the facilitation of the trial process. Consideration of dangerousness is a secondary determination once incompetency is established and the question becomes where and how to restore the person to competency: "A defendant may be found incompetent [to stand trial] if, as a result of mental disease or defect, he is unable: (a) to understand the nature of the proceedings against him; or (b) to assist and cooperate with his counsel; or (c) to participate in his defense" (6, 161.360).

Once again, "mental disease or defect" is not defined by the statutes, but it is generally interpreted by most forensic psychiatrists to mean some form of psychosis, organic mental disorder, or mental retardation. Our impression is that in Oregon relatively few persons are found incompetent to stand trial. On the other hand, Oregon appears to have a high relative rate of successful insanity defenses, which has become the object of much attention within the state.

#### The Insanity Defense

As in most jurisdictions, the insanity defense in Oregon occupies a central position in the tension between law and psychiatry. As a result of these tensions, considerable modifications have occurred over the years in relation both to the test itself and to the disposition and management of successful insanity acquittees.

A person is guilty except for insanity if, as a result of mental disease or defect at the time of engaging in criminal conduct, the person lacks substantial capacity either to appreciate the criminality of the conduct or to conform the conduct to the requirements of law.... The terms "mental disease or defect" do not include an abnormality manifested only by repeated criminal or otherwise antisocial conduct, nor do they include any abnormality constituting solely a personality disorder. (6, 161.295; emphasis added)

Forensic psychiatry has been under both severe and visible attack regarding its role in the insanity defense. There has been also considerable national debate about the insanity defense within the criminal justice system. As a result we now have experiments with abolition of the defense in Idaho (11) and Montana (12) and with the addition of a verdict of guilty but mentally ill in Michigan (13) and other jurisdictions. The verdict of guilty but mentally ill was instituted with the hope of reducing the number of successful insanity defenses by providing an alternative verdict that combined findings of guilt and mental illness. Initial experience shows that this has not taken place and that the number of successful insanity defenses remains much the same (14).

In 1978 Oregon created the Psychiatric Security Review Board (15), a parole-board-type model for monitoring insanity defense acquittees while in the hospital and/or on conditional release in the community. When the Psychiatric Security Review Board was created, the legislature did not substantially alter the insanity test that had been adopted in 1973 from the American Law Institute test. This approach to date has proved workable and acceptable to a wide variety of persons (16–20). As part of its insanity defense paper (4), APA cited the Psychiatric Security Review Board as a potential model for providing both augmented security for the general public and psychiatric treatment for the offender.

Although evidence as to the success of the Psychiatric Security Review Board existed, there was substantial pressure in the 1983 Oregon legislature to alter the system following the Hinckley verdict. After much debate, the Psychiatric Security Review Board was left intact. There were, however, two important changes made in the insanity test itself. First, the name of the verdict was changed from "not responsible because of mental disease or defect" to "guilty except for insanity." This change was made by the legislature in an attempt to more accurately characterize what happens

when a person is acquitted by reason of insanity in Oregon. In a previous paper (21) we described the sequel to acquittal as an "insanity sentence." This is now reflected in the name of the insanity verdict. The name change was also designed to reduce public confusion regarding the distinction between a finding of not guilty and a finding of insanity (22). It is not, however, synonymous with the verdict of guilty but mentally ill, which is a finding of guilt leading to a disposition within the corrections system.

The second major change in Oregon's test for insanity was to modify the second paragraph of the Oregon statute by adding a prohibition on insanity defenses based solely on any personality disorder, not just antisocial personality. There were several reasons the legislature chose to exclude the entire broad category of personality disorders. In general, insanity defenses in Oregon (19) and elsewhere (23, 24) have been successful for only the most seriously disordered individuals—those with diagnoses of psychosis, usually schizophrenia, severe organic impairment, or moderate to severe mental retardation. Personality disorders were excluded in the belief that the insanity defense should only be available for those with severe cognitive

Support for excluding defendants with personality disorders from the insanity defense came from those responsible for treating hospitalized Psychiatric Security Review Board clients. Before 1984, approximately 20% of those persons entering the insanity defense system in Oregon had been diagnosed by state hospital psychiatrists as suffering solely from personality disorders (19). It was this 20%, people with personality disorders, who were viewed as the most difficult pa-

This Oregon trend is mirrored by Rachlin et al. (25), who proposed two categories of mental conditions for forensic classification, "exculpatory and non-exculpatory mental conditions." Rachlin et al. placed individuals with personality disorders within the nonexculpatory group and viewed these individuals as ineligible for insanity defense proceedings. Eliminating the volitional arm of the American Law Institute test was recommended by APA (4) and has been adopted by Congress as part of its insanity defense modifications (26) as another means of dealing with the impulseprone individual with personality disorder without specifically excluding a whole diagnostic category from the insanity defense.

#### The Diminished Capacity Defenses

The diminished capacity defenses are poorly understood by most psychiatrists and are often confused by the press and public with the insanity defense. Diminished capacity defenses exist because of the distinction in the law between criminal act (actus rea) and criminal state of mind (mens rea). In order to find guilt, both must be proved. The degree of the crime varies not only with the seriousness of the defendant's act but

also with the culpability of the defendant's mental state. Three Oregon statutes exist in this area, one applicable to all crimes, one to crimes where substance abuse was involved, and one only in murder cases.

Mental disease or defect. A defendant may introduce expert evidence concerning his or her psychiatric condition whenever the mental illness has relevance to the mental state required by the crime: "Evidence that the actor suffered from a mental disease or defect is admissible whenever it is relevant to the issue of whether he did or did not have the intent which is an element of the crime" (6, 161.300).

If the evidence shows that the defendant did not, for example, act intentionally, he or she can be convicted only of a less severe crime. Thus, the defendant's diminished capacity to act with intent serves as a partial defense. No empirical evidence exists as to the frequency of use of this statute. Our impression is that it is used frequently as a basis for plea bargaining and much less frequently in trials.

Intoxication. The specific statutes dealing with use of alcohol and drugs are probably the most frequently used within the diminished capacity framework:

The use of drugs or controlled substances, dependence on drugs or controlled substances or voluntary intoxication shall not, as such, constitute a defense to a criminal charge, but in any prosecution for an offense, evidence that the defendant used drugs or controlled substances, or was dependent on drugs or controlled substances, or was intoxicated may be offered by the defendant whenever it is relevant to negative an element of the crime charged.

When recklessness establishes an element of the offense, if the defendant, due to the use of drugs or controlled substances, dependence on drugs or controlled substances or voluntary intoxication, is unaware of a risk of which the defendant would have been aware had the defendant been not intoxicated, not using drugs or controlled substances, or not dependent on drugs or controlled substances, such unawareness is immaterial. (6, 161.125)

Cases involving voluntary intoxication with drugs or, more commonly, alcohol have a long history of being handled within a diminished capacity framework. The intoxicated person is viewed as less responsible, or culpable, than a nonintoxicated defendant. The Oregon statute makes just such a distinction but does not allow the diminished capacity defense to reduce a crime below the level of recklessness, since becoming voluntarily intoxicated is itself viewed as reckless behavior.

Extreme emotional disturbance. In Oregon, a specific diminished capacity statute exists in relation to homicide cases. A criminal homicide is reduced from murder to first-degree manslaughter if "it is committed recklessly under circumstances manifesting extreme indifference to the value of life" (6, 163.115[2]) or it is committed by a person under the influence of an "extreme emotional disturbance," defined as follows:

A murder becomes manslaughter when the homicide is committed under the influence of extreme emotional disturbance when such disturbance is not the result of the person's own intentional, knowing, reckless or criminally negligent act, and for which disturbance there is a reasonable explanation. The reasonableness of the explanation for the disturbance shall be determined from the standpoint of an ordinary person in the actor's situation under the circumstances as the actor reasonably believes them to be. (6, 163.115[2])

Although "extreme emotional disturbance" is certainly not a recognized psychiatric diagnosis, the expert witness is called on to make such a determination. This generally means that the expert must translate the extreme emotional disturbance into a psychiatric disorder, the development of which is understandable in relation to the facts of the case. These are usually the heat-of-passion cases. These cases typically involve the disruption of relationships or a chain of events set up by factors found in the situational psychiatric disor-

#### Sentencing of Criminal Offenders

We now move from the trial phase of a criminal prosecution to the sentencing phase and focus on dangerous offender and death penalty statutes. Both statutes allow the state to increase the penalty of individuals on the basis of criteria that include the nature of the crime and the offender's past history. Both emphasize psychiatric diagnosis and the prediction of future dangerousness, thus inviting psychiatrists to enter into a very difficult area of the decisionmaking process.

The dangerous offender statute. In Oregon this statute applies to a defendant who is "being sentenced for a class A felony and the court finds that he is suffering from a severe personality disorder indicating a propensity toward criminal activity" (6, 161.725).

The statute outlines a procedure for appointing a psychiatrist to conduct an examination and provide the court with written findings and conclusions regarding the presence of this unspecified "severe personality disorder" that indicates a "propensity toward criminal activity." After hearing the case, the judge may then sentence the individual as a dangerous offender, which results in an extended prison sentence and less opportunity for parole.

The death penalty. The dangerous offender statute has similarities to the death penalty statute recently enacted in Oregon, modeled after the Texas statute. In Oregon the following determinations are required in order to sentence an individual to death.

Upon finding that the defendant is guilty of aggravated murder, the court shall conduct a separate sentencing proceeding to determine whether the defendant shall be sentenced to life imprisonment or death. The proceeding shall be conducted in the trial court before the trial jury as soon as practicable. . . .

Upon the conclusion of the presentation of the evidence, the court shall submit the following issues to the jury:

a) Whether the conduct of the defendant that caused the

death of the deceased was committed deliberately and with the reasonable expectation that death of the deceased or another would result;

b) Whether there is a probability that the defendant would commit criminal acts of violence that would constitute a continuing threat to society. In determining this issue, the court shall instruct the jury to consider any mitigating circumstances offered in evidence, including, but not limited to, the defendant's age, the extent and severity of the defendant's prior criminal conduct and the extent of the mental and emotional pressure under which the defendant was acting at the time the offense was committed; and

c) If raised by the evidence, whether the conduct of the defendant in killing the deceased was unreasonable in response to the provocation, if any, by the deceased.

The state must prove each issue submitted beyond a reasonable doubt, and the jury shall return a special verdict of "yes" or "no" on each issue considered.

The court shall charge the jury that it may not answer

any issue "yes" unless it agrees unanimously.

If the jury returns an affirmative finding on each issue considered under this section, the trial judge shall sentence the defendant to death. (6, 163.095 and 163.105 [as amended by ballot measure number 7, Nov. 6, 1984])

Psychiatric participation in dangerous offender and, most particularly, in death penalty sentences has produced, and will continue to produce, controversy that is every bit as great as in cases involving the insanity defense. The sentences imposed in both dangerous offender and death penalty statutes are based in part on psychiatrists' linking personality disorder to the long-term prediction of dangerousness. The Oregon dangerous offender statute calls on psychiatrists to say whether the person has a severe personality disorder related to a propensity toward criminal activity. Although the death penalty is less specific with regard to psychiatric diagnosis, similar factors have appeared in death penalty cases. The link between personality disorder, especially antisocial personality disorder, and the prediction of future dangerousness is a key ingredient in the imposition of the death penalty.

On the basis of studies emanating initially from the Baxstrom decision (27), Monahan (28), Cocozza and Steadman (29), and Shah (30) graphically illustrated the lack of ability of psychiatrists to predict long-term dangerous behavior. The attack on the prediction of dangerousness became more acute with the revitalization of death penalty statutes. In several Texas murder cases (31, 32) APA threw its weight as an organization against psychiatric prediction of long-term dangerousness. It should follow that if psychiatrists cannot reliably or validly predict dangerousness or link such predictions to a diagnosis of personality disorder, then psychiatrists should not participate in dangerous offender proceedings or death penalty cases. The judge or jury should make their decisions in these areas on the basis of moral reasoning rather than cloaking these decisions in a pseudo-scientific mantle.

Monahan (33) urged reexamination of the issue of the prediction of dangerousness. He characterized

what he termed "second generation thinking" regarding the prediction issue as having several themes. First is that critical review of the existing prediction research demonstrates many methodological flaws in the basic research literature in this area. There is also concern about the scope of the criticism of prediction in the research literature, suggesting that perhaps certain types of short-term predictions are more tenable than long-term predictions. Monahan also displayed guarded optimism about the future of research endeavors in this area.

Regardless of whether this is the beginning of some shift in the view of behavioral scientists in relation to the prediction of dangerousness, there remains to date no conclusive reason to suggest that clinicians can or should enter into such predictions, especially in relation to long-term issues. Diagnoses of personality disorders, in and of themselves, mean little for longterm outcome predictions of individual cases. In practice, everybody, including the psychiatrist, makes the prediction on an assumed actuarial basis applied to aggregates of individuals. The appearance of a psychiatrist, even one who is there to state the obvious, can often confuse the issue by making it look as though more is being said than anyone might know by reviewing the facts of the case. By appearing to state the obvious, forensic psychiatrists give the proceeding an air of science, although all that is happening is that the forensic psychiatrist, either intentionally or unwittingly, is inserting his or her own moral judgment into the process by way of expert testimony. This is not to say that there are no suitable roles for forensic psychiatric testimony at sentencing. There are viable sentencing roles for psychiatrists that speak to issues of mitigation (34) and rehabilitation without entering into the arena of long-term prediction of dangerous-

#### DISCUSSION

The thesis of this paper is that statutory law requires psychiatric opinion in various civil and criminal hearings and that forensic psychiatry draws much of its continuing vitality from these legal requirements. We have noted several major areas where such input is required by statute in many diverse types of hearings.

We have also discussed some of the major issues relevant to these various statutes. Currently, the most controversial areas involving forensic psychiatrists are related to the insanity defense and psychiatric involvement in death penalty cases, including, as numbers of death row inmates continue to grow, the issue of competency to be executed. These areas have brought the most criticism to the psychiatric profession from its own members, from public policy makers, and from the general public. Some areas, in particular the diminished capacity statutes, are poorly understood and often confused with insanity defenses, again contributing to an often poorly focused criticism of psychiat-

ric involvement in the courtroom. By contrast, some areas of psychiatric involvement in court activities are widely accepted. For example, although the civil commitment standards have been subject to a great deal of scrutiny and change in the last decade, not many have campaigned for removing psychiatrists from the civil commitment courtroom. Most people would consider a civil commitment hearing without psychiatric testimony unacceptable.

Finally, some of the statutory determinations have had their day of controversy and have, for the most part, passed into history. An example of this is Oregon's civil sexually dangerous person statute, which has been replaced in most cases by criminal prosecution for sexual offenders, with treatment available on a limited basis through agreements between the corrections and mental health systems.

Having noted what the law wants from psychiatry, we now briefly examine some options available to organized psychiatry in the present atmosphere of misunderstanding, criticism, and hostility. One option is total withdrawal from the legal arena. The vacuum created would be rapidly filled by other mental health professionals, who would respond to the needs of the legal system as psychiatry has attempted to do in the past. This may appeal to a certain portion of organized psychiatry, but not to all, and is thus unlikely to be either workable or enforceable.

Another theoretical approach is to change the legal system. Crimes could be determined by act alone, and a new system could be constructed that would operate without consideration for the individual's mental condition—in short, without any behavioral science in the courtroom. This position appeals to some, and bits and pieces of such change have taken place. However, these changes have fallen far short of one often-stated goal of getting psychiatrists out of the courtroom. Moreover, the concept of mental state is such an integral part of our legal heritage that it is unrealistic to consider abandoning it.

We view total withdrawal of psychiatrists from the courtroom or comprehensive change of the law as unrealistic and counterproductive responses to difficult situations. We favor instead a pick-and-choose approach to forensic psychiatry. In an earlier paper (5) we advocated viewing the practice of forensic psychiatry within a consultation framework, which allows us to respond to the demands of the law within a psychiatric context. The best option for psychiatry is to consult with the legal profession to bring psychiatric expertise to the legal arena, but only within the ethics of consultation and the limitations of knowledge in our own field (5).

The ethics of consultation are no simple matter, but we must strive to define this area as we provide consultation both in and outside of the psychiatric care system. Regarding the limitations of our knowledge, we should address diagnosis and mental state with some freedom but not play loose with legal tests. Some, like the civil commitment test, can be addressed;

others, such as the prediction of long-term dangerousness—especially as it affects life and death decisions should not be addressed given the current state of our knowledge. Where the knowledge exists, ethics should control whether we should participate at all in matters that might result in the death of the persons we examine.

In summary, since statutes will continue to call for psychiatric diagnoses, forensic psychiatrists will continue to be in demand. We are proposing a limited yet viable forensic psychiatry. As we have noted, the law and its statutory tests will not draw the line for psychiatrists. This must be done by the psychiatrists themselves, who should not provide opinions in the guise of expertise without firm scientific basis for the opinion. Failure of psychiatrists to impose limits on themselves has been the source of much of the criticism of forensic psychiatry. We believe that the approach outlined in this paper would benefit the law, its clients (who in many cases are our patients [35]), and psychiatry itself by meeting the severe challenge of the advisory system with introspection and a recognition of the limits of our knowledge.

#### REFERENCES

- Slater D, Hans VP: Public opinion of forensic psychiatry following the Hinckley verdict. Am J Psychiatry 1984; 141:675-679
- Talbott JA: Response to the presidential address: psychiatry's unfinished business in the 20th century. Am J Psychiatry 1984; 141:927–930
- Stone AA: Law, Psychiatry, and Morality: Essays and Analysis. Washington, DC, American Psychiatric Press, 1984
- Insanity Defense Work Group: American Psychiatric Association statement on the insanity defense. Am J Psychiatry 1983; 140:681-688
- 5. Bloom JD, Bloom JL: The consultation model and forensic practice. Bull Am Acad Psychiatry Law 1985; 13:159-165
- 6. Oregon Revised Statutes
- 7. State v Smith, 71 Or App 205 (1984)
- Faulkner LR, Bloom JD, McFarland B, et al: The effect of mental health system changes on civil commitment. Bull Am Acad Psychiatry Law 1985; 13:345–357
- Shore JH, Breakey W, Arvidson B: Morbidity and mortality in the commitment process. Arch Gen Psychiatry 1981; 39:930-934
- McFarland BH, Resnick M, Bloom JD: Ensuring continuity of care for a Munchausen patient through a public guardian. Hosp Community Psychiatry 1983; 34:65-67
- Idaho Code 19-207 (1) (added by S 1396, 46th Idaho Legislature, 2d regular session, 1982)
- 12. Montana Revised Codes, 45-2-101 (34), 46-14-102, 46-14-201 (1980)

- 13. Michigan Compiled Laws Annotated 768.36 (1) (adopted by Public Act 1980 of 1975)
- 14. Smith GA, Hall JA: Evaluating Michigan's guilty but mentally ill verdict: an empirical study. J Law Reform 1982; 16:77-113
- Rogers JL, Bloom JD: Characteristics of persons committed to Oregon's Psychiatric Security Review Board. Bull Am Acad Psychiatry Law 1982; 10:155–164
- Bloom JD, Rogers JL, Manson SM: After Oregon's insanity defense: a comparison of conditional release and hospitalization. Int J Law Psychiatry 1982; 5:391–402
- Rogers JL, Bloom JD, Manson SM: Insanity defenses: contested or conceded? Am J Psychiatry 1984; 141:885–888
- 18. Rogers JL, Sack WH, Bloom JD, et al: Women in Oregon's insanity defense system. J Psychiatry Law 1984; 11:515-532
- Rogers JL, Bloom JD, Manson SM: Oregon's new insanity defense system: a review of the first five years—1978–1982. Bull Am Acad Psychiatry Law 1984; 12:359–379
- Rogers JL, Bloom JD, Manson SM: Oregon's Psychiatric Security Review Board: a comprehensive system for managing insanity acquittees. Annals of the American Academy of Political and Social Science 1986; 484:86–99
- Rogers JL, Bloom JD: The insanity sentence: Oregon's Psychiatric Security Review Board. Behav Sci Law 1985; 3:69–84
- 22. Rogers JL: Clear—except for confusion. Oregon State Bar Bulletin 1984; 44(5):25-26
- 23. Petrilla J: The insanity defense and other mental health dispositions in Missouri. Int J Law Psychiatry 1982; 5:81-101
- Pasewark RA: Insanity plea: a review of the research literature.
   J Psychiatry Law 1981; 9:357-401
- Rachlin S, Halpern AL, Portnow SL: The volitional rule, personality disorders and the insanity defense. Psychiatr Annals 1984; 14(2):139-147
- 26. 18 United States Code, section 20
- 27. Baxstrom v Herold, 383 US 107, 86 S Ct 760 (1966)
- Monahan J: The Clinical Prediction of Violent Behavior: DHHS Publication ADM 81-921. Rockville, Md, National Institute of Mental Health, 1981
- Cocozza J, Steadman HJ: The failure of psychiatric predictions of dangerousness: clear and convincing evidence. Rutgers Law Review 1976; 29:1074–1101
- Shah SA: Dangerousness: conceptual, prediction, and public policy issues, in Violence and the Violent Individual. Edited by Hays JR, Roberts TK, Solway KS. New York, SP Medical & Scientific Books, 1981
- 31. Estelle v Texas, 451 US 454 (1981)
- 32. Barefoot v Estelle, 103 S Ct 3383 (1983)
- Monahan J: The prediction of violent behavior: toward a second generation of theory and policy. Am J Psychiatry 1984; 141:10–15
- Bloom JD, Bloom JL: An examination of the use of transcultural data in the courtroom. Bull Am Acad Psychiatry Law 1982; 30:437-440
- 35. Bloom JD, Faulkner LR, Shore JH, et al: The young adult chronic patient and the legal system: a systems analysis, in Effective Aftercare for the 1980s: New Directions for Mental Health Services 19. Edited by Cutler DL. San Francisco, Jossey-Bass. 1983

# Serum Prolactin Levels in Sons of Alcoholics and Control Subjects

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The authors evaluated changes in serum prolactin levels as a measure of differences in response to ethanol between 30 healthy, drinking, young adult sons of alcoholics and 30 matched control subjects with no family history of psychiatric or substance abuse problems. The control subjects were matched for demographic variables, drug use histories, and alcohol use histories. Each individual was tested on three occasions, receiving, in random order, placebo, 0.75 ml/kg of ethanol, and 1.1 ml/kg of ethanol. Controlling for baseline prolactin measures and hormonal changes after placebo, the authors found that the sons of alcoholics had significantly lower prolactin levels in response to the high-dose ethanol challenge.

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ur laboratory is searching for trait or vulnerability markers of a predisposition toward alcoholism (1, 2). We have focused on young adult sons of alcoholic fathers (subjects with a positive family history) in recognition of their three- to fourfold higher risk for the future development of this disorder (2, 3). We have compared these healthy, higher-risk young men with carefully matched control subjects who have no known family history of psychiatric or substance abuse problems (subjects with a negative family history).

One consistent finding has been a lower intensity of reaction to ethanol in the sons of alcoholics. Despite similar ratings after placebo, following ingestion of active alcohol doses, subjects with a positive family history reported significantly less intense feelings of intoxication than those with a negative family history (4–6), a finding corroborated in two other laboratories (7, 8). In our studies (9), subjects with a positive family history also had lower postethanol scores on tests measuring changes in cognitive and motor performance, such as standing steadiness (body sway), than did those with a negative family history.

Changes in subjective feelings and levels of performance after drinking, however, could be influenced by many factors other than genetic predisposition. Therefore, we have searched for more biological and less subjective markers of the intensity of reaction to drinking. To be of maximal value, these biological measures should be relatively simple and noninvasive, inexpensive, reliable, and easy to repeat during the test sessions, and they must be likely to change following the doses of ethanol used in our research paradigm. One biological measure that meets these criteria is the

plasma level of prolactin (10-12).

In work published in 1983 (11), we observed the plasma level of prolactin after administration of a single dose of 0.75 ml/kg of ethanol in 44 pairs of subjects with positive or negative family histories of alcoholism (88 men). We documented an increase in this hormone after ethanol administration for both family-history groups but a more rapid return to pre-ethanol challenge levels and below for the positivefamily-history group during the 3-hour experimental period. The most impressive group difference for plasma level of prolactin was seen 150 minutes after ethanol administration. Although consistent with our prediction of less intense or more transitory changes in plasma level of prolactin after ingestion of ethanol for the positive-family-history group, the results were considered preliminary for two reasons. First, the absence

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of a placebo session did not allow us to control for the effects of time, expectancy, and nonspecific testing stresses. The second limitation was the problem inherent in attempting to understand a phenomenon while observing reactions after only one ethanol test dose.

The investigation reported in this paper was an attempt to expand on the 1983 study by using another group of matched pairs of subjects with positive or negative family histories and adding a placebo session and a second ethanol challenge session.

#### **METHOD**

Subjects were identified through a structured questionnaire sent to all male students and nonacademic staff 21–25 years old at the University of California, San Diego. The 70% who responded were paid \$3 to supply demographic information and data on past history of medical and psychiatric problems, drinking and drug use patterns and problems, and any history of psychiatric disorders in themselves and first-degree relatives. All potential subjects who already fulfilled DSM-III criteria for alcoholism, drug abuse, or any other major psychiatric disorder or who had any major medical problem were excluded from the sample.

The remaining individuals were placed in the positive-family-history category if the questionnaire or subsequent interview indicated that they had a biological father who met DSM-III criteria for alcoholism. Each of the 30 men with this positive family history was matched for age, race, religion, educational level, recent drinking history, drug use history, and heightto-weight ratio with a control subject without a history of alcoholism, drug abuse, or major psychiatric disorder in any first- or second-degree relative. Each individual was then brought to the laboratory on three occasions, where he received, in random order (with the same sequence for each member of a pair), placebo (3 ml of ethanol floated on top of a mixer), 0.75 ml/kg of 95% ethanol, or 1.1 ml/kg of 95% ethanol. Active drinks were administered as a 20% by volume solution in a sugar-free, noncaffeinated, carbonated beverage consumed over 10 minutes.

For all sessions, men arrived at 7:00 a.m. after a 10-hour fast and underwent baseline cognitive and psychomotor testing. Then an 18-gauge scalp-vein needle attached to a heparin lock was inserted in an antecubital vein. At approximately 9:00 a.m. and a minimum of 30 minutes after the venipuncture, baseline blood samples were drawn, the beverage was administered, and the subject was tested for approximately 3 hours. Blood samples were taken for measurement of blood alcohol level and plasma level of prolactin approximately every half-hour. Blood alcohol levels were analyzed by using the head-space technique on a gas chromatograph with a flameionization detector. Plasma level of prolactin was measured with a direct plasma assay kit obtained from Immunex (San Diego, Calif.) using an antibody with a cross-reactivity with follicle-stimulating hormone (FSH) of 1.0%, with thyroid-stimulating hormone (TSH) of 0.3%, with leutinizing hormone (LH) of 0.1%, and with human growth hormone (GH) of 0.1%. The procedure has a detection limit of 3 ng/ml and intraassay and interassay coefficients of variation of 8% and 10%, respectively (13).

The major differences between family-history groups in plasma levels of prolactin over time were analyzed in two ways. First, to evaluate placebo results we used a two-factor, mixed-model, repeated-measures analysis of covariance in which subjects were nested with respect to the "between" factor (family history) and crossed with respect to the "within" factor (time). Although baseline measures did not differ significantly between family-history groups or across sessions, they correlated with postbaseline values and so were used as covariates in all analyses.

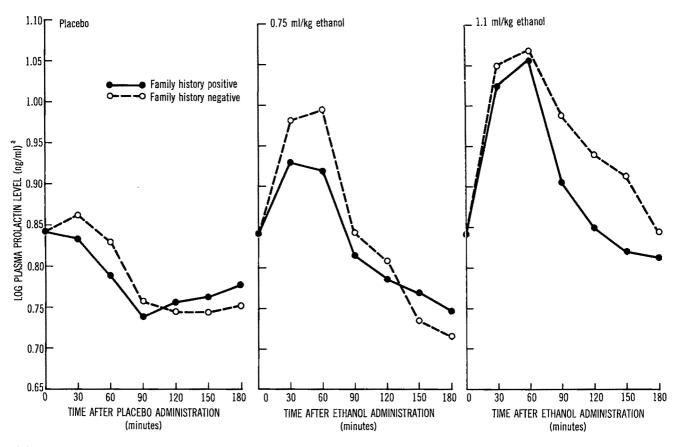
The second major type of analysis was carried out to directly compare placebo values with results from each active dose. We considered treating family history as a "within" factor (a randomized block design) in a repeated measures analysis. This approach would have been most appropriate if there were significant levels of intrapair correlation for plasma level of prolactin. The absence of a consistent significant correlation between groups of subjects with positive or negative family histories dictated that the most conservative statistical approach was to use a mixed model, treating our family-history groups as statistically independent. Thus, we carried out two separate three-factor, mixedmodel, repeated-measures analyses of covariance (placebo versus low dose and placebo versus high dose) with dose as an additional "within" factor. All results are reported as means ± SDs.

#### **RESULTS**

Complete data were available on 30 Caucasian pairs of subjects with positive or negative family histories (60 men). The mean age of these men was  $22.2\pm1.75$ years, and their history of alcohol intake over the previous 6 months included drinking on 8.3±5.06 days per month and consuming 3.0±1.08 drinks per occasion. The blood alcohol levels after the two active ethanol doses were similar for the positive-familyhistory group (58.0 $\pm$ 8.13 and 96.2 $\pm$ 11.53 mg/dl (milligrams of ethanol per 100 ml of blood) and for the negative-family-history group (57.2±6.99 and 91.3± 12.32 mg/dl) after low and high ethanol doses, respectively. An analysis of variance (ANOVA) comparing the positive-family-history group and the negativefamily-history group after both doses revealed no significant differences.

Baseline raw plasma prolactin values for the placebo, low-dose, and high-dose sessions were also similar for the positive-family-history group  $(6.54\pm2.54, 6.49\pm1.96, \text{ and } 6.58\pm2.14 \text{ ng/ml})$  and the negative-family-history group  $(6.27\pm2.49, 5.87\pm1.77, \text{ and})$ 

FIGURE 1. Changes in Plasma Prolactin Levels in Response to Placebo and Low- and High-Dose Ethanol Challenge in 30 Men With and 30 Matched Control Subjects Without a Family History of Alcoholism



<sup>&</sup>lt;sup>a</sup>Plasma prolactin levels log transformed and adjusted for baseline values by analysis of covariance.

TABLE 1. Analyses of Covariance for Changes in Plasma Prolactin Levels in Response to Placebo and Low- and High-Dose Ethanol Challenge in 30 Men With and 30 Matched Control Subjects Without a Family History of Alcoholism

		Analyses											
Factor		Placebo			w-Dose Eth	anol	High-Dose Ethanol						
	F	df	p	F	df	p	F	df	р				
Main effects													
Time	26.51	5, 290	<.01	92.51	5, 290	<.001	43.31	5, 290	<.01				
Dose		•		26.04	1,57	<.01	82.07	1,57	<.01				
Family history	0.18	1,57	.67	1.09	1,57	.30	2.90	1,57	.09				
Interactions		•			•			•					
Dose × Time				35.96	5, 290	<.01	12.89	5, 290	<.001				
Family History × Time	3.04	5, 290	.01	6.36	5, 290	<.01	0.69	5, 290	.63				
Dose × Family History		•		0.11	1,57	.74	1.60	1,57	.21				
Dose × Family History × Time				0.86	5, 290	.51	2.26	1,57	$<.05^{a}$				

<sup>&</sup>lt;sup>a</sup>Significant by post hoc analysis.

6.04±2.73 ng/ml). The two-factor repeated-measures ANOVA for the log-transformed baseline values over the three sessions revealed no significant differences. Overall, using Pearson's r for the 60 men in the sample, we found that baseline placebo prolactin levels correlated with low-dose baseline prolactin levels at .67 (p<.001) and with high-dose baseline prolactin levels at .65 (p<.001) and that low-dose baseline plasma levels correlated with high-dose baseline pro-

lactin levels at .69 (p<.001).

Figure 1 presents the mean log-transformed plasma levels of prolactin for the two family-history groups following placebo, low-dose, and high-dose challenges. The values have been log transformed to correct for departures from normality expected with this pulsatile hormone, and the data were adjusted by means of analyses of covariance to reflect any minor group differences at baseline.

Figure 1 shows that plasma levels of prolactin for both groups decreased during the first 90 minutes after placebo administration (falling off more rapidly for the positive-family-history group), after which there was a leveling off or slight increase. The two-factor analysis of covariance results presented in table 1 for placebo reveal that there was a significant change in hormone levels over time but that the family-history groups did not differ significantly following placebo. Although there was a significant interaction between family history status and time, post hoc tests of simple main effects (14) revealed no significant group differences at any individual time point.

As shown in figure 1, following the low-dose ethanol challenge both family-history groups demonstrated an increase in plasma levels of prolactin at 30 and 60 minutes, after which there was a rapid decrease in values over the remaining experimental period. Using placebo versus low dose ethanol in the three-factor analysis of covariance outlined in table 1, we found that among the main effects there was a significant change in plasma level of prolactin over time and a significant dose effect, although when placebo and low-dose data over time were combined the family history effect alone was not significant. Looking at interactions, we found significant Dose by Time and Family History by Time interactions, but after the time points were collapsed, the two family-history groups did not show significant differences over the two doses (Dose by Family History interaction). The triple interaction of Dose by Time by Family History was not significant. In summary, there is evidence that the overall plasma prolactin response following low-dose ethanol was significantly different from plasma prolactin values following placebo. However, despite the trend for lower plasma levels of prolactin for the positive-family-history group after the low dose, this trend was not significant when changes after placebo were considered.

As demonstrated in figure 1, the changes in plasma level of prolactin following the high-dose ethanol challenge were greater than those observed following the low-dose challenge. Both family-history groups showed a sharp increase in plasma level of prolactin at 30 and 60 minutes, after which values returned toward baseline; there was a more rapid decrease for the positive-family-history group than for the negativefamily-history group. The results of the three-factor analysis of covariance comparing prolactin levels after high-dose challenge with those after placebo are also shown in table 1. Among main effects, there were significant time and dose effects, but combining the two doses and all time points revealed that the plasma level of prolactin values for the two groups were not significantly different. Looking at interactions, we found that the Dose by Time interaction was significant, but the Family History by Time and the Dose by Family History interactions were not. Important for our consideration was the documentation of a significant triple interaction between dose, family history,

and time. Using the post hoc test of simple interaction effects (14) and concentrating on the time point that had best differentiated groups in our 1983 data, we found a significant group difference at 150 minutes (F=5.60, df=1, 347, p<.02). Additional post hoc analyses revealed differences between the two groups at 120 minutes as well (F=4.50, df=1, 347, p=.03), although because of appropriate adjustments in alpha levels for post hoc tests this was not statistically significant. In summary, statistical analyses of the data from figure 1 revealed that plasma prolactin values were significantly different during high-dose and placebo sessions and that, even after placebo results were considered, hormone levels for the two family groups became significantly different at 150 minutes following the high-dose ethanol challenge.

There was also a significant ethanol dose effect on plasma levels of prolactin between low-dose and high-dose challenges. Among main effects, family history approached significance (F=3.43, df=1, 57, p=.07), while dose (F=35.71, df=1, 57, p<.001) and time (F=76.16, df=5, 290, p<.001) were significant. For interactions, the Dose by Time by Family History interaction was significant (F=3.80, df=5, 290, p=.002), and post hoc tests revealed that the difference at 150 minutes was significant (F=7.50, df=1, 347, p=.006).

To this point in the analyses we have used the most demanding statistics, comparing plasma levels of prolactin during the entire 3 hours. One potential problem with this approach, however, is that equal emphasis is placed on hormone increases and decreases. It is possible that such analyses could contribute to a type II error and that group differences in the acute plasma prolactin response to ethanol could be missed. Therefore, we carried out an additional series of analyses.

First, we invoked Student's t test to determine if the maximum log-transformed plasma prolactin values reached in each test condition were significantly different for the two family-history groups, after adjusting for any baseline differences. Although the positive-family-history group and the negative-family-history group did not differ significantly on this measure after placebo (t=-0.34, df=58, p=.74) or after high-dose ethanol (t=-0.87, df=58, p=.38), the plasma prolactin levels of the negative-family-history group did increase significantly more than those of the positive-family-history group following the low-dose challenge (t=-1.97, df=58, p=.05).

Second, we compared the mean positive prolactin values over the 180 minutes for the two family-history groups in the three test conditions after subtracting baseline values (15). These results showed that the changes after placebo were small, with no family-history group differences. In contrast, the active dose data revealed a nonsignificant trend for group differences following low-dose challenge (t=-1.51, df=58, p=.14) and a significant group difference following high-dose challenge (t=-2.38, df=58, df=58

also indicated a significantly greater increase in plasma level of prolactin for the negative-family-history group (t=-0.258, df=58, p=.01).

#### DISCUSSION

These results document another important difference in response to ethanol between positive-family-history and negative-family-history matched pairs. Both this study and our 1983 study generally revealed lower postethanol plasma levels of prolactin for the positive-family-history group, despite similar hormone values at baseline, with the most impressive difference at 150 minutes after drinking.

Inspection of figure 1 could lead to two different (although not mutually exclusive) interpretations. The trend observed after the low-dose challenge might indicate that the negative-family-history group responded more intensely with higher plasma levels of prolactin during the first hour following a modest ethanol challenge. After the high dose, on the other hand, the groups demonstrated similar increases in plasma level of prolactin, but the positive-familyhistory group appeared to have adapted more rapidly to the presence of ethanol, showing a faster decrease in plasma level of prolactin during the test session. It is also possible that the high dose of ethanol was high enough so that both family-history groups demonstrated their maximal prolactin response and that only after the blood alcohol levels began to fall did the group differential become apparent. A different research paradigm using multiple ethanol test doses during a single session is required to answer if either of these explanations is correct.

The patterns of changes in plasma level of prolactin after ethanol administration were similar in this study and in the 1983 study. However, in the earlier investigation significant differences were observed after a low dose, while the data presented here revealed the greatest differential between family-history groups following a high dose. It is possible that the overall group difference after a low dose might have become significant if our study of 30 pairs had been expanded to 44 pairs, as were used in 1983, or that we may have seen even a greater group difference if a high dose had also been used in the earlier study. The inconsistency, however, suggests that although both studies document a potentially important difference between positive-family-history and negative-family-history matched pairs in their response to ethanol, the precise nature of the group difference in postethanol plasma levels of prolactin and its relationship to ethanol dose is not fully understood.

The information reported here is important for a number of reasons. First, the lower plasma levels of prolactin after ethanol for the positive-family-history group are consistent with our measures of postethanol subjective feelings, decrements in cognitive and psychomotor performance, and changes in cortisol levels in sons of alcoholics (5, 6, 9, 16, 17). It is reassuring that the results from yet another biological system indicate that the two family-history groups respond differently to modest ethanol doses.

A second important aspect of these data is the potential power that postethanol plasma levels of prolactin might add to a multivariate approach used to identify individuals at highest risk for alcoholism. Although the concurrence between our 1983 results and those of the present study is impressive, the level of statistical significance of the differences between positive-family-history and negative-family-history groups is modest. Therefore, when used alone, it is not likely that plasma level of prolactin will be an exceptionally sensitive marker associated with differences in ethanol response between family-history groups. However, preliminary analyses indicate that changes in plasma level of prolactin might not correlate closely with most other measures of ethanol response, including subjective intoxication, changes in electrophysiological and cognitive/psychomotor performance, and alterations in cortisol levels. Thus, plasma level of prolactin might be tapping a relatively distinct dimension of differences between positive-family-history and negative-familyhistory groups.

Third, the prolactin data may serve another important purpose in the future. Meltzer (10) has suggested that the study of hormonal responses in individuals with various psychiatric diagnoses might be a "window" to neurochemical changes in the brain and the pituitary gland. It is possible that study of a combination of prolactin and other neurohormones might help us to understand more about the relationship between ethanol-induced neurotransmitter changes and the risk for the future development of alcoholism.

Finally, the data presented here corroborate the change in plasma prolactin levels following challenges with clinically relevant doses of ethanol, regardless of family history. The levels of this hormone dropped over time during the placebo session, a finding consistent with the testing of subjects in the early morning, soon after awakening (12). However, hormone changes after low-dose ethanol were significantly different from those after placebo, and plasma levels of prolactin following high-dose ethanol were significantly different from values following both placebo and the low-dose ethanol challenge. Unfortunately, the present study sheds little light on the neurochemical mechanisms contributing to the increase in plasma level of prolactin following ethanol administration. We were addressing the more limited question of whether this hormone changed in our test paradigm, whether the change was different after the two ethanol doses, and whether the amount of change differed for the two family-history groups.

#### REFERENCES

 Schuckit MA: Studies of populations at high risk for alcoholism. Psychiatr Dev 1985; 3:31–63

- Schuckit MA: Genetics and the risk for alcoholism. JAMA 1985; 254:2614–2617
- Goodwin DW: Alcoholism and genetics. Arch Gen Psychiatry 1985; 42:171–174
- Schuckit MA: Peak blood alcohol levels in men at high risk for the future development of alcoholism. Alcohol: Clinical and Experimental Research 1981; 5:64-66
- Schuckit MA: Subjective responses to alcohol in sons of alcoholics and controls. Arch Gen Psychiatry 1984; 41:879–884
- Schuckit MA: Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. J Stud Alcohol 1980; 41:242-249
- O'Malley SS, Maisto SA: The effects of family drinking history on responses to alcohol: expectancies and reactions to intoxication. J Stud Alcohol 1985; 46:289–297
- 8. Pollock VE, Teasdale TW, Gabrielli WF, et al: Subjective and objective measures of response to alcohol among young men at risk for alcoholism. J Stud Alcohol 1986; 47:297–304
- Schuckit MA: Ethanol-induced changes in body sway in men at high alcoholism risk. Arch Gen Psychiatry 1985; 42:375–379
- Meltzer HY: Prolactin and psychiatry (editorial). Am J Psychiatry 1981; 138:1203–1206

- Schuckit MA, Parker DC, Rossman LR: Prolactin responses to ethanol in men at elevated risk for alcoholism and controls. Biol Psychiatry 1983; 18:1153-1159
- de la Fuente J-R, Rosenbaum AH: Prolactin in psychiatry. Am J Psychiatry 1981; 138:1154–1160
- Mooradian AD, Morley JE, Korchik WP, et al: Comparison between bioactivity and immunoreactivity of serum prolactin in uraemia. Clin Endocrinol 1985; 22:241–247
- Kirk RE: Experimental Design: Procedures for the Behavioral Sciences. Belmont, Calif, Wadsworth, 1968
- 15. Schuckit MA, Gold E, Risch S: The search for hormonal markers of the risk for alcoholism, in Proceedings of the Third Congress of the International Society for Biomedical Research on Alcoholism. Edited by Lindros K, Ylikahri R. New York, Pergamon Press (in press)
- Schuckit MA: Differences in plasma cortisol after ethanol in relatives of alcoholics and controls. J Clin Psychiatry 1984; 45:374–379
- 17. Schuckit MA, Gold E, Risch SC: Plasma cortisol following ethanol in sons of alcoholics and controls. Arch Gen Psychiatry (in press)

# Platelet Membrane Fluidity in Alzheimer's Disease and Major Depression

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Double-blind fluorescence studies of platelet membrane fluidity were conducted at 37°C for 51 patients with Alzheimer-type dementia, 24 nondemented depressed patients, and 50 neurologically healthy subjects. The fluidity of the hydrocarbon region of platelet membranes from the demented group, as reflected by the steady-state anisotropy of the fluorescent probe 1,6-diphenyl-1,3,5-hexatriene (DPH), was significantly greater than that for the depressed and normal control subjects. Within the demented group, platelet membrane fluidity was significantly correlated with severity of dementia but not with duration of illness or age at onset. Demented patients with "increased" platelet membrane fluidity had an earlier onset, were more severely demented, and deteriorated more rapidly. (Am J Psychiatry 1987; 144:860-868)

ounting evidence suggests that Alzheimer's disease is accompanied by pathologic changes in cells outside the CNS (1, 2). Abnormalities in nonneural cells of patients with Alzheimer's disease have been reported in platelets (3–6), RBCs (7–16), granulocytes (17, 18), lymphocytes (19–27), cultured skin fibroblasts (28–31), and adrenal medullary cells (32). Several of thse abnormalities—including our initial observation that platelet membranes of patients with

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Alzheimer's disease exhibited increased membrane fluidity, as revealed by fluorescence studies with the probe 1,6-diphenyl-1,3,5-hexatriene (DPH) (5, 6) suggest that Alzheimer's disease is accompanied by alterations in the structure or function of cell membranes from nonneural as well as neural tissues. In support of this possibility, abnormalities of cell membrane composition and structure have been found in brain tissue obtained at autopsy from patients with confirmed Alzheimer's disease who have died. These include changes in brain phospholipid metabolism, as revealed by 31P nuclear magnetic resonance spectroscopy (33, 34), disordering of cortical myelin, as indicated by X-ray diffraction studies (35), and an alteration in the molecular dynamics of hippocampal membranes, as shown by fluorescence spectroscopy (36).

It is difficult to study brain diseases, and it is currently impossible to establish the diagnosis of Alzheimer's disease before postmortem examination of brain tissue. Given these problems, the impact of a reliable and specific antemortem peripheral tissue marker for Alzheimer's disease would be substantial. Such a marker would not only serve as a clue to the biological basis of Alzheimer's disease but would also improve clinical research on the epidemiology and treatment of the disorder by allowing accurate diagnosis while the patient is alive. The reliability of the finding of abnormal platelet membrane fluidity in Alzheimer's disease has already been suggested by its replicability in our studies and those of other investigators (N. Hicks et al., personal communication). The specificity of the finding has not been established. Abnormalities of peripheral tissues, including abnormalities of cell membranes, receptors, and enzymes of blood elements, have been reported in CNS diseases as diverse as Huntington's chorea (37-39), multiple sclerosis (40, 41), and affective illness (42-48). This raises the question of whether any such abnormalities are disease specific or whether they are all merely general phenomena associated with CNS dysfunction or chronic illness.

To begin to address this question, we compared membrane characteristics of platelets isolated from 51 demented patients with probable Alzheimer's disease, 24 nondemented depressed patients, and 50 neurologically healthy control subjects. Depressed patients were chosen as a comparison group to control for the nonspecific effects associated with debilitating mental illness. In addition, depression and dementia share some syndromic features, and the differential diagnosis of these two illnesses is not always clear (49). Finally, it has been reported that membrane characteristics of blood elements are abnormal in depressed patients (42–48), making depressed patients an excellent comparison group for testing the specificity of the association of altered membrane fluidity to Alzheimer's disease. Analyses of membrane fluidity were performed at 37°C with DPH and 1-[4-(trimethylamino) phenyl]-6-phenyl-1,3,5-hexatriene (TMADPH), which label the membrane hydrocarbon region and lipidaqueous interface, respectively (50, 51). The resulting biophysical characteristics of corresponding membrane preparations were compared among the drugfree, age- and sex-matched diagnostic groups, and their relationship to demographic variables and clinical severity was examined.

#### **METHOD**

The study sample consisted of 125 subjects who were at least 45 years of age. A complete history was taken, and each subject underwent a physical examination and detailed neurological, psychiatric, and mental status examinations. All subjects had normal results on CBC, urinalysis, blood chemistry screen, and thyroid function tests and had normal serum folate and B<sub>12</sub> levels. None of them were suffering from malnutrition or vitamin deficiency syndromes, as determined by clinical and laboratory evaluation. Individuals with disorders that affect blood cell membrane lipid composition or serum lipid profiles-including alcohol or other substance abuse, generalized atherosclerosis, familial lipidoses, diabetes mellitus, uremia, and nephrosis—and those who were on restrictive diets were excluded from the study (50, 52, 53).

The control group consisted of 50 neurologically healthy volunteers. The Alzheimer's disease group consisted of 51 outpatients with "probable" Alzheimer's disease as defined by NINCDS-ADRDA criteria (54). Individuals who had any history of treatment with neuroleptic or antidepressant drugs or who were currently being treated with any medication that can affect platelet membrane fluidity by in vitro or in vivo exposure were excluded from these two groups (55-58). In addition, all patients remained free of any drug ingestion, including the use of aspirin, for at least 24 hours before blood was drawn. Forty-eight of the 50 control subjects and 44 of the 51 demented patients were not receiving any prescribed medications. The medications taken by the remaining subjects at the time of entry into the study were primarily diuretics and/or digitalis derivatives. The clinical diagnosis of probable Alzheimer's disease was made conjointly by a neurologist and a psychiatrist on the basis of the

insidious onset of dementia with progression in the absence of other systemic or brain diseases that may cause dementia. Each demented patient received both a CAT scan and an EEG. Findings on either test that suggested focal neurological disease served as additional exclusion criteria. Patients who experienced delusions, hallucinations, or seizures only after the onset of dementia were not excluded. The age at onset of symptoms of dementia was determined to the nearest year according to a history provided by the patient, the patient's family, and the treating physician. Duration of illness was determined by subtracting the patient's age at onset from the age at the time blood was drawn. The degree of cognitive impairment was graded by use of the Mini-Mental State (59) score (0=worst, 30=best) and the Dementia Rating Scale (60) score (0=best, 28=worst).

A total of 24 elderly, depressed nondemented inpatients were included as a comparison group. All subjects in this group met the criteria of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (61) and the Research Diagnostic Criteria (62) for major depressive disorder (primary, unipolar, or nondelusional), met DSM-III criteria for major depression without psychotic features, and had Hamilton Rating Scale for Depression (63) scores of 15 or more (single rater, first 17 items). To exclude patients with dementia, a Mini-Mental State score of 26 or more also served as a criterion for inclusion in this group. Patients in this group were medication free for at least 2 weeks before blood was drawn. All subjects provided written informed consent before they were admitted to the study. For demented patients, written informed consent was also obtained from a family member.

Blood drawing and platelet isolation were performed according to a minor modification of the method of Corash and co-workers (64), which typically results in platelet yields of 95%-99%. A 20-ml fasting blood sample from each subject was drawn between the hours of 9:00 a.m. and 12:00 noon by antecubital venipuncture through a 19-gauge needle into a plastic syringe. Ten-milliliter volumes were then transferred to each of two polypropylene plastic tubes (Falcon) containing 25 mg of tetrasodium EDTA dihydrate and mixed by repeated inversion. In addition to its role as an anticoagulant, EDTA inhibited potential proteolysis during processing. So that all platelet processing and subsequent analyses would be carried out by personnel who were blind to the diagnoses, anticoagulated blood samples were coded by the clinical staff before transport to the laboratory.

All platelet isolation procedures were conducted at room temperature to minimize platelet adherence to other blood cells, as previously described (58). Final platelet yields were greater than 90% in all cases. Transmission electron micrographs of the platelet preparations revealed less than 0.5% contamination by red cells and leukocytes. Total platelet membranes were prepared from platelet suspensions as previously described (6, 55–57).

TABLE 1.	Demographic and Clinic	al Characteristics of Patie	nts With Probable Al	Izheimer's Disease and of	f Depressed and Normal Control
Subjects					

	Sex			ears)			77 11 D
Group	M	F	Mean	SD	Mini-Mental State Score	Dementia Rating Scale Score	Hamilton Depression Scale Score
Patients with probable Alzheimer's disease (N=51)	17	34	68.6	8.0	Mean±SD= 16.8±4.7	Mean±SD= 7.3±4.6	<15
Depressed control subjects (N=24)	8	16	68.8	<b>7.4</b>	≥27		Mean±SD= 23.6±3.8
Healthy control subjects (N=50)	18	32	66.7	9.4	≥27	_	<15

Platelet membranes were diluted to a final optical density of 0.03 at 600 nm. Ten-milliliter suspensions of each were labeled by the addition of 10  $\mu$ l of 1-mM solutions of DPH or TMADPH in dimethylformamide. Labeling was carried out in the dark at final probe concentrations of 1  $\mu$ M for 60 minutes at 37°C (50, 55–58, 65, 66). Labeled membranes contained approximately one probe molecule to 100 phospholipid molecules.

Fluorescence measurements were performed on an SLM 4800 spectrofluorometer equipped as previously described (58). All measurements were made at 37.0°±0.1°C, with stirring. Corrected fluorescence spectra were obtained for each sample at  $37.0^{\circ} \pm 0.1^{\circ}$ C, and spectra characteristic of DPH and TMADPH were observed in each case. The excitation and emission maxima for the DPH-labeled preparations occurred at  $359.5\pm0.5$  nm and  $427.5\pm0.5$  nm, respectively, while those for TMADPH-labeled preparations occurred at  $362.0\pm0.0$  nm and  $427.5\pm0.5$  nm, respectively. For steady-state anisotropy measurements, the spectrofluorometer was configured in the T format, labeled membranes were excited at 360 nm, and emission light was measured through Schott long pass filters. Fluorescence lifetimes were measured by the phase-modulation method (67), with excitation frequencies of 6, 18, or 30 MHz, an excitation slit width of 0.5 nm, a of 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP) in ethanol as a lifetime standard ( $\tau$ =1.35 nsec), and the emission polarizer oriented at 55°.

Autofluorescence produced by unlabeled suspensions was negligible, as was the minimal signal produced by residual aqueous probe. Excitation light scattering was negligible, as determined by the steadystate anisotropy of serial dilutions of labeled membranes. Mean lifetimes determined from phase angle measurements were 1.0 nsec or less shorter than the corresponding values determined from modulation measurements. This is typical for biological membranes labeled with these probes and most likely reflects the coexistence of membrane domains of differing composition and structure (50, 68, 69).

Apparent probe rotation rates (R) were calculated from steady-state anisotropy values (r) and fluorescence lifetime measurements (7) according to the Perrin equation (70), with 0.395 as the limiting anisotropy value (r<sub>0</sub>) of both DPH and TMADPH (51, 71). Fluorescence lifetimes obtained from phase angle measurements at 18 MHz were used in these calculations.

A decrease in steady-state anisotropy in the presence of a constant fluorescence lifetime reflects an increase in apparent probe rotational rate. Because the rotation of DPH and TMADPH in biological membranes is anisotropic, the calculated apparent rotational rates are the result of a prominent component reflecting the range of probe motion as well as a component reflecting the rate of motion (71–74). Regardless of this limitation in the ability to interpret calculated rotation rates, the steady-state anisotropy measurements provide a reliable, valid index of membrane "fluidity" or "order" over the range of values reported (55, 75–78).

For continuous variables, comparisons of corresponding values between groups were made by one-way analyses of variance with post hoc two-tailed t tests. For between-group comparisons of categorical variables, the chi-square statistic or Fisher's exact test was used. Relationships between continuous variables were explored by means of the parametric Pearson correlation coefficient. All comparisons that revealed statistically significant differences according to the t test remained significant when examined by the nonparametric Mann-Whitney test. Likewise, those pairs of variables for which the Pearson correlation coefficient was significantly different from zero were also related by a statistically significant Spearman (nonparametric) correlation coefficient of the same sign.

#### **RESULTS**

Platelet Membrane Fluidity in Alzheimer's Disease and Depression

The clinical characteristics of the three diagnostic groups—the patients with probable Alzheimer's disease, the depressed patients, and the healthy control subjects—are presented in table 1. The three groups were well matched for age and sex. The patients in the Alzheimer's disease group were moderately demented on average; their mean±SD age at the onset of symptoms was  $66.0\pm7.8$  years, and the mean±SD duration of their illess was  $4.9\pm2.2$  years.

Steady-state anisotropy value and fluorescence lifetimes, determined at 37.0°±0.1°C, are presented in table 2 and figure 1. The steady-state anisotropy of DPH in labeled platelet membranes differed significantly among the diagnostic groups, as determined by

TABLE 2. Fluorescence Properties of Platelet Membranes Labeled With DPH or TMADPH for Patients With Probable Alzheimer's Disease and for Depressed and Normal Control Subjects

		DPH	ł <sup>a</sup>		TMADPH <sup>b</sup>					
	Steady Anisotrop	Fluorescence Lifetime (nsec) <sup>c</sup>		Steady-State Anisotropy Value <sup>c</sup>		Fluorescence Lifetime (nsec) <sup>c</sup>				
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Patients with probable Alzheimer's disease (N=51)	0.1920 <sup>d</sup>	0.0080	8.5	0.3	0.2516	0.0033	4.7	0.3		
Depressed control subjects (N=24)	0.1982	0.0048	8.4	0.5	0.2517	0.0048	4.7	0.2		
Healthy control subjects (N=50)	0.1991	0.0058	8.5	0.3	0.2517	0.0032	4.7	0.3		

<sup>a</sup>DPH=1,6-diphenyl-1,3,5-hexatriene.

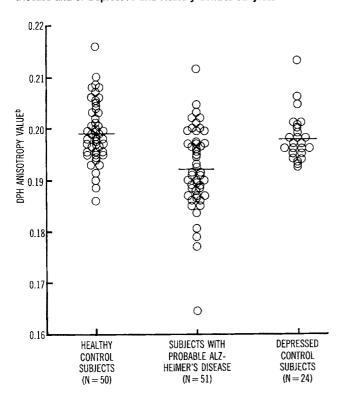
<sup>b</sup>TMADPH=1-[4-(trimethylamino)phenyl]-6-phenyl-1,3,5-hexatriene.

groups, respectively.

dSignificant difference between the Alzheimer's disease patients and the depressed control subjects and between the Alzheimer's disease patients

and the healthy control subjects (p=.01, Tukey multiple comparison procedure).

FIGURE 1. Steady-State Anisotropy Values (at 37°C) of DPH-Labeled Platelet Membranes of Patients With Probable Alzheimer's Disease and of Depressed and Healthy Control Subjects



<sup>a</sup>DPH=1,6-diphenyl-1,3,5-hexatriene. <sup>b</sup>Group means are marked by horizontal bars.

a one-way analysis of variance (F=16, df=2, 122, p<.0001). The mean steady-state anisotropy value of DPH in platelet membranes for the demented group, 0.1920, was significantly lower than the respective means for the healthy control group, 0.1991, and the depressed group, 0.1982 (p=.01, Tukey multiple comparision procedure). The mean DPH anisotropy values for the healthy and depressed control groups

did not differ significantly from each other. Analysis of variance did not reveal a significant effect of diagnostic group on the fluorescence lifetime of DPH in these labeled platelet suspensions. Since DPH localizes preferentially within the hydrocarbon core of lipid membranes, these results indicate that dementia of the Alzheimer type is associated with an increase in the fluidity (inversely related to anisotropy) of the hydrocarbon core of platelet membranes. However, major depression in the elderly was not associated with a significant alteration in this biophysical characteristic of platelet membranes.

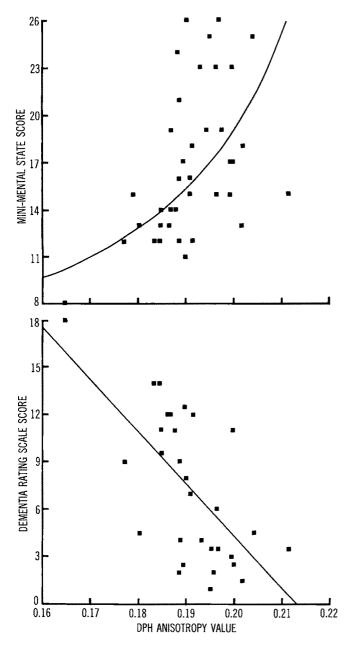
In contrast to the findings with DPH, analysis of variance did not reveal a significant effect of diagnostic group on either the steady-state anisotropy or the fluorescence lifetime of TMADPH in labeled platelet membranes from the study sample. Since TMADPH is anchored to the lipid aqueous interface of labeled membranes, these results imply a selective alteration in molecular dynamics at the hydrocarbon region of platelet membranes of patients with Alzheimer-type dementia that does not extend superficially to affect the lipid-aqueous interface at 37°C.

#### Relationship of Platelet Membrane Alteration to Clinical Characteristics of the Demented Patients

The observed increase in platelet membrane fluidity, as reflected by a reduction in the steady-state anisotropy of DPH-labeled membranes, was significantly correlated with clinical severity as measured by either the Mini-Mental State score or the Dementia Rating Scale score. As shown in figure 2, Mini-Mental State scores and DPH anisotropy values were best related by a reciprocal model of the form 1/Y = a + bX, where Y = Mini-Mental State score, X = DPH anisotropy value,  $a \pm SE = 0.306 \pm 0.054$ , and  $b \pm SE = -1.26 \pm 0.28$ . The associated correlation coefficient was -.60 (1/Y versus X,  $p = 7.9 \times 10^{-5}$ ). Dementia Rating Scale scores and DPH anisotropy values were best related by a linear model of the form Y = a + bX,

cSteady-state anisotropy and fluorescence lifetime (phase, 18 MHz) measurements were made at 37.0°±0.1°C. Mean apparent DPH rotation rates (calculated) were 2.10×10<sup>8</sup>sec<sup>-1</sup> (SD=0.21×10<sup>8</sup>), 2.01×10<sup>8</sup>sec<sup>-1</sup> (SD=0.37×10<sup>8</sup>), and 1.93×10<sup>8</sup>sec<sup>-1</sup> (SD=0.13×10<sup>8</sup>) for the demented, depressed, and healthy control groups, respectively. Mean apparent TMADPH rotation rates (calculated) were 2.04×10<sup>8</sup>sec<sup>-1</sup> (SD=0.13×10<sup>8</sup>), 2.04×10<sup>8</sup>sec<sup>-1</sup> (SD=0.11×10<sup>8</sup>), and 2.07×10<sup>8</sup>sec<sup>-1</sup>(SD=0.20×10<sup>8</sup>) for the demented, depressed, and healthy control groups, respectively.

FIGURE 2. Relationship of Steady-State Anisotropy Values (at 37°C) of DPH-Labeled<sup>a</sup> Platelet Membranes and Severity of Dementia for Patients With Probable Alzheimer's Disease<sup>b</sup>



<sup>a</sup>DPH=1,6-diphenyl-1,3,5-hexatriene. <sup>b</sup>Decreasing Dementia Rating Scale scores reflect decreasing severity of dementia. Decreasing anisotropy values and Mini-Mental State scores reflect increasing membrane fluidity and increasing severity of dementia, respectively.

where Y=Dementia Rating Scale score, X=DPH anisotropy value,  $a\pm SE=70.3\pm14.5$ , and  $b\pm SE=-330\pm76$ . The associated correlation coefficient was -.64 (Y versus X, p= $1.6\times10^{-4}$ ). The magnitude and statistical significance of both correlations were increased by the inclusion of the most severely demented patient in the group. However, even after the exclusion of this outlier, the correlations remained statistically

significant (although the respective correlation coefficients decreased in magnitude). Regardless of the analysis performed, the degree of the observed alteration in platelet membrane fluidity paralleled the severity of dementia as reflected by either the Mini-Mental State score or the Dementia Rating Scale score.

In contrast to clinical severity, neither age at onset nor duration of illness was significantly correlated with the steady-state anisotropy of DPH in labeled platelet membranes of the patients with Alzheimer-type dementia. Moreover, the mean±SD DPH steady-state anisotropy value for labeled platelets of the patients with a presenile onset of symptoms (before age 65; N=25), 0.1911±0.0082, although lower, did not differ significantly from the corresponding mean±SD value for those patients whose onset of symptoms occurred in the senium (at 65 years of age or older; N=26), 0.1935±0.0083.

Although we have previously reported a statistically significant positive correlation of the steady-state anisotropy of DPH in labeled platelets with the age of healthy subjects from the second to the ninth decade, the correlation of these variables within the healthy control group in this study did not reach statistical significance (r=.12, p=.18). This apparent discrepancy most likely resulted from the narrower age range of the healthy control subjects in this study.

Analysis of variance revealed a trend for the sex of the patient to affect the steady-state anisotropy of DPH in labeled platelets within the study population (.05<p<.10). No significant effect of sex on the fluorescence lifetime of DPH was observed in the total study sample or within any of the three diagnostic groups. Finally, as expected, the mean steady-state anisotropy of DPH-labeled platelet membranes of the seven demented patients who were taking medications that met our inclusion criteria did not significantly differ from that of the 44 patients who had not been treated with medications at the time of entry into the study.

## Characteristics of Demented Patients With "Normal" or "Increased" Platelet Membrane Fluidity

Inspection of the scattergram of DPH anisotropy values for labeled platelets of the patients with Alzheimer-type dementia suggested a bimodal distribution with a nadir near the mean for the entire group, 0.1920. The lower 5th percentile of DPH anisotropy values among the control subjects (healthy and depressed), corresponding to those less than 0.1920, was defined as "increased" platelet membrane fluidity. This cutoff is similar to that from a previous study in which 0.1916 was selected retrospectively as an estimate of the lower limit of the "normal" range of values for healthy, unmedicated subjects in this age group (79). Since the fluorescence anisotropy of DPH-labeled platelet membranes did not exhibit a significant correlation with subjects' age above 45 years, age correction

TABLE 3. Demographic and Clinical Characteristics of Patients With Probable Alzheimer's Disease Who Had "Normal" or "Increased" Platelet Membrane Fluidity

Characteristic	Patients Wi Fluidity (DPI value≥0.193	I anisotropy	Patients Wit Fluidity (DPI value<0.192	I anisotropy	•		
	Mean	SD	Mean	SD	(df=49) <sup>a</sup>	р	
DPH anisotropy value	0.1987	0.0042	0.1862	0.0057	Antonia		
Age (years)	71.7	8.2	66.0	7.1	2.67	.01 <sup>b</sup>	
Age at onset (years)	69.0	8.7	63.6	5.9	2.54	.02 <sup>b</sup>	
Mini-Mental State score	19.5	4.3	15.1	4.1	3.72	.001	
Dementia Rating Scale score	3.8	2.6	9.6	4.3	5.94	.0001	
Duration of illness (years)	4.0	2.3	4.3	2.1	0.48	.60 <sup>b</sup>	

<sup>&</sup>lt;sup>a</sup>Comparisons of corresponding means were made by two-tailed t tests.

of the proposed cutoff value was unnecessary. Twenty-eight (55%) of the 51 demented patients were in the increased fluidity subgroup, while 23 (45%) were in the normal fluidity group. With 0.1920 as the cutoff value, only four (8%) of the 50 healthy control subjects and none of the depressed control subjects had DPH anisotropy values outside the normal range.

The characteristics of the demented patients in the subgroups with normal or increased platelet membrane fluidity are presented in table 3. The mean DPH anisotropy value for the normal fluidity subgroup, 0.1987, was very similar to the means for both the healthy and the depressed control groups. The mean age of patients in the increased fluidity subgroup, 66.0 years, was significantly less than that of the normal fluidity subgroup. The sex ratios of the subgroups nine men and 14 women in the normal fluidity group and eight men and 20 women in the increased fluidity group—were similar to one another and to the sex ratio for the entire demented group. The mean age at onset of dementia for the patients in the increased fluidity subgroup, 63.6 years, was significantly less than that for the normal fluidity subgroup. The patients in the increased fluidity subgroup were also more severely affected at the time of their entry into the study—as reflected by their significantly lower mean Mini-Mental State score and significantly higher mean Dementia Rating Scale score—than the patients in the normal fluidity subgroup. Since the two subgroups did not differ with respect to mean duration of illness, these data imply that the subgroup with increased fluidity suffered a more rapid decline on average than did the patients in the normal fluidity subgroup. In summary, the subgroup of patients with Alzheimertype dementia who manifested increased platelet membrane fluidity (DPH anisotropy value of less than 0.1920) were younger at the time of clinical onset, were more severely demented, and suffered from a more rapid progression of their illness than the patients in the normal fluidity group. Moreover, stratification by normal or increased platelet membrane fluidity did not significantly affect the sex ratio of either subgroup. An autopsy was performed on one of the 51 patients with Alzheimer-type dementia who

died after completion of this study, and the neuropathologic diagnosis of Alzheimer's disease was confirmed. The steady-state anisotropy value for DPH-labeled platelet membranes of this patient, 0.1886, was in the range of the increased fluidity subgroup.

#### **DISCUSSION**

The results confirm and extend the findings of our preliminary reports of a platelet membrane abnormality associated with Alzheimer's disease. An increase in platelet membrane fluidity, as reflected by a significant decrease in the steady-state anisotropy of DPH-labeled membranes, has now been reported by us for groups of patients with Alzheimer's disease in Boston and Pittsburgh (5, 6) and by others for patients in London (N. Hicks et al., personal communication). Initial assessments of the specificity of this platelet membrane characteristic are promising. The increase in platelet membrane fluidity associated with Alzheimer's disease was not found in platelets of patients with depression, a common cause of reversible dementia in the elderly (49, 80); mania (56), which may also be accompanied by a secondary dementia (81); or multi-infarct dementia (N. Hicks et al., personal communication). In addition, we previously reported that platelet membrane fluidity decreases from the second to the ninth decade in neurologically healthy control subjects (82). Therefore, our findings do not support the hypothesis that Alzheimer's disease results from a pathological acceleration of the normal aging process. The weight of the available evidence suggests that the increase in platelet membrane fluidity associated with Alzheimer's disease may be due to a dysregulation of platelet membrane biogenesis or turnover that results in the accumulation of internal platelet membranes (58, 79).

None of several possible sources of artifact that we considered could account for the observed increase in platelet membrane fluidity associated with Alzheimer's disease. Investigator bias was eliminated by ensuring that the laboratory staff remained blind to clinical data and, conversely, that clinicians remained blind to the biophysical data. Fasting blood samples were used to

<sup>&</sup>lt;sup>b</sup>Bonferroni corrected type I value=0.0083.

minimize the possible effects of eating, even though we have found no effect of the ingestion of single meals on the platelet membrane characteristics measured. While the isolation of different subpopulations of platelets from the comparison samples was a potential source of bias, platelet yields for the samples were greater than 90% in all cases. None of the patients was receiving treatment with medications that affect platelet membrane fluidity, including neuroleptics and antidepressants, and none of the demented patients or control subjects had any reported history of exposure to such medications. Furthermore, it is unlikely that our findings would have resulted from unreported exposure to these medications on the basis of the effects that these agents have on the physical properties of cell membranes. Phenothiazines increase the steady-state anisotropy of DPH-labeled platelet membranes, while haloperidol and tricyclic antidepressants have no effect on this platelet membrane characteristic at clinically relevant concentrations (36, 55-58, 83). Finally, the increase in platelet membrane fluidity associated with Alzheimer's disease did not appear to result from nonspecific effects of chronic illness, since 1) the steady-state anisotropy of DPH-labeled platelet membranes from the demented group was not significantly correlated with duration of illness, 2) none of the patients in the study was suffering from malnutrition or vitamin deficiency syndromes that often accompany chronic debilitation, and 3) depression in the elderly that was sufficiently disabling to warrant hospitalization was not accompanied by an increase in platelet membrane fluidity.

Historically, dementia in the elderly has been separated into forms with presentle onset (before age 65) or senile onset (at age 65 or older). This distinction was based largely on the clinical observation that patients who developed symptoms of dementia at an early age often had a more rapid decline and more often had family members with dementia than those whose symptoms developed later in life. In our study, the characteristics of the demented subgroup with increased platelet membrane fluidity bore a resemblance to the classification "presenile" dementia, made on clinical grounds. These patients exhibited an earlier onset of symptoms, were more severely demented as measured by Mini-Mental State and Dementia Rating Scale scores, and suffered a more rapid deterioration than patients with normal platelet membrane fluidity. Also, preliminary evidence suggests that this group with abnormal membrane fluidity may have a greater family history of dementia. Family studies are now underway that will determine whether increased platelet membrane fluidity has potential as a marker for familial (possibly inherited) dementia of the Alzheimer type.

#### REFERENCES

- Blass JP, Zemcov A: Alzheimer's disease: a metabolic systems degeneration? Neurochem Pathol 1984; 2:103-114
- 2. Blass JP, Hanin I, Barclay L, et al: Red blood cell abnormalities

- in Alzheimer's disease. J Am Geriatr Soc 1985; 33:401-405
- 3. Smith RC, Ho BT, Kralik P: Platelet monoamine oxidase in Alzheimer disease. J. Gerontol 1982; 37:572-574
- Ksiezak-Reding H, Murphy C, Blass JP: Enzyme activities in platelets from patients with Alzheimer's disease. Age 1983, 6:11
- Zubenko GS, Cohen BM, Growdon J, et al: Cell membrane abnormality in Alzheimer's disease (letter). Lancet 1984; 2:235
- Zubenko GS, Cohen BM: Biophysical alterations in cell membranes associated with psychotherapeutic drug exposure, psychopathology, and aging. Psychophamacol Bull 1985; 21:631– 640
- Markesbery WR, Leung PK, Butterfield DA: Spin label and biochemical studies of erythrocyte membranes in Alzheimer's disease. J Neurol Sci 1980; 45:323–330
- Chipperfield B, Newman PM, Moyes ICA: Decreased erythrocyte cholinesterase activity in dementia (letter). Lancet 1981; 2: 199
- Friedman E, Sherman KA, Ferris SH, et al: Clinical response to choline plus piracetam in senile dementia: relation to red cell choline levels. N Engl J Med 1981; 304:1490–1491
- Barclay LL, Blass JP, Kopp U, et al: Red-cell/plasma choline ratio in dementia (letter). N Engl J Med 1982; 307:501
- 11. Perry RH, Wilson ID, Bober MJ, et al: Plasma and erythrocyte acetylcholinesterase in senile dementia of Alzheimer type (letter). Lancet 1982; 1:174–175
- Smith RC, Ho BT, Hsu L, et al: Cholinesterase enzymes in the blood of patients with Alzheimer's disease. Life Sci 1982; 30: 543-546
- Diamond JM, Matsuyama SS, Meier K, et al: Elevation of erythrocyte countertransport rates in Alzheimer's dementia (letter). N Engl J Med 1983; 309:1061–1062
- McHarg A, Naylor CH, Ballinger BR: Erythrocyte ouabain binding in dementia. Gerontology 1983; 29:140–144
- Hanin I, Reynolds CF III, Kupfer DJ, et al: Elevated red blood cell/plasma choline ratio in dementia of the Alzheimer type: clinical and polysomnographic correlates. Psychiatry Res 1984; 13:167–173
- Butterfield DA, Nicholas MM, Markesbery WR: Evidence for an increased rate of choline efflux across erythrocyte membranes in Alzheimer's disease. Neurochem Res 1985; 10:909– 918
- Fu TK, Kessler JO, Jarvik LF, et al: Philothermal and chemotactic locomotion of leukocytes: method and results. Cell Biophys 1982; 4:77–95
- 18. Jarvik LF, Matsuyama SS, Kessler JO, et al: Philothermal response of polymorphonuclear leukocytes in dementia of the Alzheimer type. Neurobiol Aging 1982; 3:93–99
- Nordenson I, Adolfsson R, Beckman G, et al: Chromosomal abnormality in dementia of Alzheimer type (letter). Lancet 1980; 1:481-482
- Miller AE, Neighbour PA, Katzman R, et al: Immunological studies in senile dementia of the Alzheimer type: evidence for enhanced suppressor cell activity. Ann Neurol 1981; 10:506– 510
- 21. Krause LJ: Decreased natural killer cell activity in Alzheimer disease. Neurosciences Abstracts 1982; 9:115
- Moorhead PS, Heyman A: Chromosome studies of patients with Alzheimer disease. Am J Med Genet 1983; 14:545

  –546
- 23. Robbins JH, Otsuka F, Tarone RE, et al: Radiosensitivity in Alzheimer disease and Parkinson disease (letter). Lancet 1983; 1:468-469
- 24. Ebstein RP, Oppenheim G, Stessman J: Alzheimer's disease: isoproterenol and prostaglandin E<sub>1</sub>-stimulated cyclic AMP accumulation in lymphocytes. Life Sci 1984; 34:2239–2243
- Fischman HK, Reisberg B, Albu P, et al: Sister chromatid exchanges and cell cycle kinetics in Alzheimer's disease. Biol Psychiatry 1984; 19:319–327
- Oppenheim G, Mintzer J, Halperin Y, et al: Acute desensitization of lymphocyte beta-adrenergic-stimulated adenylate cyclase in old age and Alzheimer's disease. Life Sci 1984; 35: 1795–1802
- Skias D, Bania M, Reder AT, et al: Senile dementia of Alzheimer's type (SDAT): reduced T8-cell-mediated suppressor activ-

- ity. Neurology 1985; 35:1635-1638
- Andria-Waltenbaugh AM, Puck TT: Alzheimer disease: further evidence of a microtubular defect. J Cell Biol 1977; 75:279
- Sorbi S, Blass JP: Fibroblast phosphofructokinase in Alzheimer's disease and Down's syndrome. Banbury Report 1983; 15: 297
- Mowshowitz SL, Dawson GJ, Elizan TS: Antiviral response of fibroblasts from familial Alzheimer's disease and Down's syndrome to human interferon-alpha. J Neural Transm 1983; 57: 121-126
- Peterson C, Gibson GE, Blass JP: Altered calcium uptake in cultured skin fibroblasts from patients with Alzheimer's disease (letter). N Engl J Med 1985; 312:1063–1065
- Averback P: Two new lesions in Alzheimer's disease (letter).
   Lancet 1983; 2:1203
- Pettegrew JW, Minshew NJ, Cohen MM, et al: P-31 NMR changes in Alzheimer's and Huntington's disease brain (abstract). Neurology 1984; 34:281
- 34. Barany M, Chang Y, Arus C, et al: Increased glycerol-3-phosphorylcholine in post-mortem Alzheimer's brain (letter). Lancet 1985; 1:517
- 35. Chia LS, Thompson JE, Moscarello MA: X-ray diffraction evidence for myelin disorder in brain from humans with Alzheimer's disease. Biochim Biophys Acta 1984; 775:308–312
- Zubenko GS: Hippocampal membrane alteration in Alzheimer's disease. Brain Res 1986; 385:115-121
- Belendink K, Belendink GW, Freedman DX: Blood monoamine metabolism in Huntington's disease. Arch Gen Psychiatry 1980; 37:325-332
- 38. Butterfield DA, Markesbury WR: Huntington's disease: a generalized membrane defect. Life Sci 1981; 28:1117–1131
- 39. Pettegrew JW, Nichols JS, Stewart RM: Membrane studies in Huntington's disease. J Neurochem 1981; 36:1966–1976
- Seaman GVF, Swank RL, Tamblyn CH, et al: Simplified red-cell electrophoretic mobility test for multiple sclerosis. Lancet 1979; 1:1138–1139
- 41. Fraser KB, Millar JHD, Haire M, et al: Increased tendency to spontaneous in vitro lymphocyte transformation in clinically active multiple sclerosis. Lancet 1979: 2:715-717
- active multiple sclerosis. Lancet 1979; 2:715-717
  42. Extein I, Tallman J, Smith CC, et al: Changes in lymphocyte beta-adrenergic receptors in depression and mania. Psychiatry Res 1979; 1:191-197
- Schliefer SJ, Keller SE, Meyerson AT, et al: Lymphocyte function in major depressive disorder. Arch Gen Psychiatry 1984; 41:484-486
- 44. Wolfe N, Cohen BM, Gelenberg AJ: Alpha 2 adrenergic receptors in platelet membranes of depressed patients. Psychiatry Res (in press)
- Cohn CK, Dunner DK, Axelrod J: Reduced catechol-o-methyltransferase activity in red blood cells of women with primary affective disorder. Science 1970; 170:1323–1324
- Pettegrew JW, Nichols JS, Minshew NJ, et al: Membrane biophysical studies of lymphocytes and erythrocytes in manicdepressive illness. J Affective Disord 1982; 4:237–247
- 47. Goekoop JG, Wisse DM, Van Brussel JL, et al: Decreased erythrocyte membrane elevations in patients with a major depressive episode. J Affective Disord 1984; 7:273–280
- Hitzemann RJ, Hirschowitz J, Garver DL: On the physical properties of red cell ghost membranes in the affective disorders and psychoses. J Affective Disord 1986;10:227-232
- Post F: Dementia, depression, and pseudodementia, in Psychiatric Aspects of Neurologic Disease. Edited by Benson DS, Blumer D. New York, Grune & Stratton, 1975
- Shinitzky M, Barenholz Y: Fluidity parameters of lipid regions determined by fluorescence polarization. Biochim Biophys Acta 1978; 515:367-394
- 51. Prendergast FG, Haughland RP, Callahan PJ: 1-[4-(trimethylamino)phenyl]-6-phenylhexa-1,3,5-triene: synthesis, fluorescence properties, and use as a fluorescence probe of lipid bilayers. Biochemistry 1981; 20:7338–7345
- Bacchus H: Essentials of Metabolic Diseases and Endocrinology. Baltimore, University Park Press, 1976, pp 81–120
- 53. Hunt WA: Alcohol and Biological Membranes. New York,

- Guilford Press, 1985, pp 14-40
- 54. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-944
- 55. Zubenko GS, Cohen BM: Effects of phenothiazine treatment on the biophysical properties of platelet membranes from psychiatric patients. Biol Psychiatry 1985; 20:384–396
- 56. Zubenko GS, Cohen BM: Effects of psychotropic agents on the physical properties of platelet membranes in vitro. Psychopharmacology 1985; 86:369-373
- Zubenko GS, Cohen BM: A cell membrane correlate of tardive dyskinesia in patients treated with phenothiazines. Psychopharmacology 1986; 88:230-236
- 58. Zubenko GS, Malinakova I, Chojnacki B: Proliferation of internal membranes in platelets from patients with Alzheimer's disease. J Neuropathol Exp Neurol (in press)
- Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198
- Blessed G, Tomlinson BE, Roth M: The association between quantitative measures of dementia and senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968; 114:797-811
- Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
- 62. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
- Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62
- 64. Corash L, Tan H, Gralnick HR: Heterogeneity of human whole blood platelet subpopulations, I: relationship between buoyant density, cell volume, and ultrastructure. Blood 1977; 49:71–87
- 65. Kuhry JG, Duportail G, Bronner C, et al: Plasma membrane fluidity measurements on whole living cells by luorescence anisotropy of trimethylammoniumdiphenylhexatriene. Biochim Biophys Acta 1985; 845:60–67
- 66. Simons E, Whitin JC, Morinelli TA, et al: Membrane fluidity and platelet fibrinogen receptor exposure by proteolytic enzymes. Thromb Res 1985; 39:91–96
- 67. Spenser RD, Weber G: Measurements of subnanosecond fluorescence lifetimes with a cross-correlation phase fluorometer. Ann NY Acad Sci 1969; 158:361–376
- 68. Karnovsky MJ, Kleinfeld AM, Hoover RL, et al: The concept of lipid domains in membranes. J Cell Biol 1982; 94:1-6
- Barrow DA, Lentz BR: Membrane structural domains: resolution limits using diphenylhexatriene fluorescence decay. Biophys J 1985; 48:221-234
- 70. Weber G: Polarization of the fluorescence of macromolecules, l: theory and experimental method. Biochem J 1952; 51:145-155
- Kinosita K, Kawato S, Ikegami A: A theory of fluorescence polarization decay in membranes. Biophys J 1977; 20:289–305
- 72. Lakowicz JR, Prendergast FG, Hogen D: Differential polarized phase fluorometric investigations of diphenylhexatriene in lipid bilayers: quantitation of hindered depolarizing rotations. Biochemistry 1979: 18:508-519
- chemistry 1979; 18:508-519
  73. Mantulin WW, Weber G: Rotational anisotropy and solvent-fluorophore bonds: an investigation by differential polarized phase fluorometry. J Chemical Physics 1977; 66:4092-4099
- Lakowicz JR, Prendergast FG: Quantitation of hirdered rotations of diphenylhexatriene in lipid bilayers by differential polarized phase fluorometry. Science 1978; 200:1399–1401
- 75. Heyn MP: Determination of lipid order parameters and rotational correlation times from fluorescence depolarization experiments. FEBS Lett 1979; 108:359-364
- Jahnig F: Structural order of lipids and proteins in membranes: evaluation of fluorescence anisotropy data. Proc Natl Acad Sci USA 1977; 76:6361–6365
- 77. Van Blitterswijk WJ, Van Hoeven RP, Van der Meer BW: Lipid

- structural order parameters (reciprocal of fluidity) in biomembranes derived from steady-state fluorescence polarization measurements. Biochim Biophys Acta 1981; 644:323–332
- 78. Pottell H, Van der Meer BW, Herreman W: Correlation between the order parameter and the steady-state fluorescence anisotropy of 1,6-diphenyl 1,3,5-hexatriene and an evaluation of membrane fluidity. Biochim Biophys Acta 1983; 730:181–186
- 79. Zubenko GS, Cohen BM, Boller F, et al: Platelet membrane abnormality in Alzheimer's disease. Ann Neurol (in press)
- Grunhaus L, Dilsaver S, Greden JF, et al: Depressive pseudodementia: a suggested diagnostic profile. Biol Psychiatry 1983; 18:215–225
- 81. Thase ME, Reynolds CF: Manic pseudodementia. Psychosomatics 1984; 25:256–260
- 82. Cohen BM, Zubenko GS: Aging and the biophysical properties of cell membranes. Life Sci 1985; 37:1403-1409
- Zimmer G, Schulze P: Membrane action of tricyclic drugs. Arzneimittelforschung 1981; 31:1389–1392

## Biogenic Amine and Metabolite Levels in Depressed Patients With High Versus Normal Hypothalamic-Pituitary-Adrenocortical Activity

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The activity of the hypothalamic-pituitary-adrenocortical (HPA) axis is often high in depressive illness. The authors studied 132 depressed patients and 80 healthy control subjects. They report a significant direct association between HPA axis activity and adrenomedullary epinephrine secretion in depressed patients. They also found that depressed patients with high HPA activity tend to have lower CSF levels of 5-hydroxyindoleacetic acid, a serotonin metabolite, and modestly lower levels of 3-methoxy-4-hydroxyphenylglycol, a metabolite of epinephrine and norepinephrine, than patients with normal HPA activity. These findings provide potentially important leads for understanding interactions of biogenic amine systems with HPA axis function.

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A multicenter study of the biology of depression, the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression: Biological Studies (1, 2), measured hypothalamic-pitu-

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itary-adrenocortical (HPA) axis function and CSF levels of the neurotransmitter metabolites 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA) in 132 depressed patients and 80 age-matched healthy control subjects. The 24-hour urinary excretion of norepinephrine, epinephrine, normetanephrine, metanephrine, vanillylmandelic acid (VMA), and MHPG was also measured in these same patients. For the most part, previous large-sample studies have focused on analyses of single systems. One aim of this multisystem approach was to provide further development of an understanding of linkages in the altered functioning of HPA and aminergic systems in depressed patients. This aim initially derived in part from the generally recognized influence of central norepinephrine and more recently other aminergic systems on corticotropinreleasing hormone (CRH) release. Animal data have strengthened the rationale for combined HPA and biogenic amine system studies in that epinephrine infused at physiological rates has been reported to produce pituitary-adrenal activation in rats (3). Prior reports from this multicenter study indicate that depressed patients as a group have high urinary excretion of epinephrine and norepinephrine (4, 5).

In this study we examined a possible linkage between high adrenomedullary function, as measured by high urinary epinephrine excretion, and the high HPA function that has been observed repeatedly in a substantial proportion of depressed patients (6–8). We also examined the relationship in depressed patients

between high HPA activity and CSF levels of 5-HIAA and MHPG.

#### **METHOD**

The data analyzed for this report were obtained from depressed patients and healthy normal control subjects. The explicit details of the experimental protocol for this study have been published elsewhere (9). We studied 132 patients with primary major depressive disorder of sufficient severity to require admission to a hospital for treatment and 80 age-matched healthy control subjects. Diagnoses were made according to the Research Diagnostic Criteria from data obtained with an interview instrument, the Schedule for Affective Disorders and Schizophrenia (10).

After an initial medical and psychiatric examination, patients who were free of major medical illness and who met the diagnostic inclusion criteria were started on a placebo regimen and entered into a 14-day, drug-free study period after their informed consent had been obtained. During this baseline, drug-free study phase, 24-hour urine specimens were collected and subsequently assayed for urinary free cortisol, norepinephrine, epinephrine, normetanephrine, metanephrine, VMA, and MHPG. Urinary free cortisol was measured by a radioimmunoassay method (11) and urinary catecholamines and metabolites by spectrophotofluorometric and gas-liquid chromatographic methods (4). An average of values from 2 successive days of 24-hour urine collections (study days 9 and 10), assayed separately, was used to determine the baseline values of biogenic amines and their metabolites. To assure completeness of the 24-hour urine collections, urinary creatinine was assayed and evaluated in relation to the following criteria for creatinine excretion: for women, 14-21 mg/kg of body weight per 24 hours, and for men, 21-28 mg/kg of body weight per 24 hours. If the creatinine level for a 24-hour specimen did not fall within  $\pm 20\%$  of these limits for the normative range or if it varied more than 20% from day to day, the urine sample was excluded from analysis. In a few cases, backup urine collections obtained on days 7 and 8 did meet the criteria and were analyzed instead.

After the 24-hour urine collections and after the subjects had 8 hours of overnight rest, a CSF sample was obtained. The sample was obtained by means of a lumbar puncture performed on study day 11 between 8:30 and 9:30 a.m., before food intake, with the subject in the sitting position. This sample was assayed for MHPG, HVA, and 5-HIAA with gas chromatographic/mass spectrometric techniques (4). Baseline plasma coritsol levels obtained before and at 8:30 a.m., 4:00 p.m., and 10:30 p.m., as part of a dexamethasone suppression test (DST), were measured by radioimmunoassay (11). The DST was performed by administering orally, under direct nursing supervision, 1 mg of dexamethasone in liquid form at 11:00 p.m.

on study day 12, immediately after the end of a 24-hour urine collection for determination of the basal urinary free cortisol level.

While urinary amines were measured on days 9 and 10 and basal urinary free cortisol was measured on day 12, HPA function appeared stable over this period. Plasma cortisol was measured at 8:30 a.m. on days 9, 10, and 12 in depressed patients; paired t-test comparisons showed no significant difference in mean level for any day. Plasma cortisol measured at 8:30 a.m. on day 12 correlated significantly with the mean of 8:30 a.m. measures on days 9 and 10 (r=.68, N=111, p=.0001). Urinary amine levels did not differ significantly on days 9 and 10 (paired t tests).

#### **RESULTS**

We first examined the relationship between type of DST response and measures of biogenic amines and their metabolites. A postdexamethasone level of at least 5 µg/dl at 8:30 a.m. was chosen to define DST nonsuppression, on the basis of the bimodal distribution of postdexamethasone morning plasma cortisol levels and in view of the relatively high levels of 4:00 p.m. postdexamethasone cortisol in some of the agematched healthy control subjects (11). Because there were significant male-female differences and effects of age on some amine levels in this group of depressed patients (4), comparisons between DST suppressors and nonsuppressors were made on amine levels adjusted for age and sex by analysis of covariance. Mean CSF 5-HIAA levels were significantly lower in 23 depressed DST nonsuppressors than in 62 suppressors (table 1). No other statistically significant difference was detected in mean levels of the eight other monoamine measures obtained, although there were trends for nonsuppressors to have lower mean CSF levels of HVA and MHPG (table 1) and urinary MHPG (F=3.02, df=1, 94, p=.09). Mean urinary epinephrine excretion tended to be higher in 29 nonsuppressors than in 52 suppressors (p=.10, table 1). Differences between suppressors and nonsuppressors in urinary excretion of norepinephrine, normetanephrine, metanephrine, and VMA did not approach statistical significance.

We next examined the relationship of basa! urinary free cortisol excretion, an integrated measure of HPA activity over a 24-hour period, to the amine/metabolite values in urine and CSF. In depressed patients urinary free cortisol excretion was significantly correlated with urinary epinephrine (r=.42, N=70, p=.0003). There was a significant difference in epinephrine excretion between unipolar and bipolar depressed subjects (4); however, an analysis of covariance on urrrary epinephrine levels in these depressed patients indicated that the effect of urinary free cortisol remained significant after covariance for the effect of diagnostic subgroup on urinary epinephrine (F=11.79, df=1, 67, p=.0001). Urinary free cortisol did not correlate sig-

nificantly with any other amine measured in urine or CSF. (Weak correlations were noted with urinary norepinephrine [r=.19, N=73, p=.10] and CSF 5-HIAA [r=-.18, N=69, p=.13].)

Subjects were divided into cortisol "normosecreting" and "hypersecreting" groups according to whether basal urinary free cortisol excretion exceeded 133 µg/day (mean+1.28 SD of the healthy control level), a level seen in only 7% of age-matched healthy control subjects (11). Urinary free cortisol hypersecretors had a higher mean urinary excretion of epinephrine (p=.0004, table 1). The positive association of urinary epinephrine and urinary free cortisol was not the result of incomplete urine collections in some patients, causing low epinephrine and cortisol in the same urine samples. Nearly identical results were obtained when urinary free cortisol hypersecretors and normosecretors were compared in terms of urinary epinephrine excretion divided by creatinine excretion (F=10.85, df=1, 66, p=.002, for analysis of covariance analogous to that in table 1, column 1, row 2). Urinary free cortisol hypersecretors had lower mean CSF levels of 5-HIAA (p=.02) and MHPG (p=.06), adjusted for age and sex, than did normosecretors (table 1). Mean differences in CSF levels of HVA and urinary levels of norepinephrine, metanephrine, normetanephrine, MHPG, and VMA did not approach statistical significance in analogous mean comparisons with age and sex covariates.

To further test the relationship between HPA system function and amine and metabolite values, we derived two groups of subjects from the depressed patients who were clearly different in their level of HPA axis activity. Group 1, with high HPA activity, consisted of the 18 depressed patients who were both DST nonsuppressors and cortisol hypersecretors (basal urinary free cortisol higher than 133 µg/day). Group 2, with normal HPA activity, consisted of the 48 depressed patients who were DST suppressors and had a basal urinary free cortisol excretion of 133 µg/day or less. The high and low groups differed in two other HPA measures: basal morning plasma cortisol level (mean±  $SD=20.5\pm6.2$  versus  $15.0\pm5.3$  µg/dl; t=3.43, df=62, p=.001) and basal CSF cortisol level (10.7 $\pm$ 1.1 versus  $8.9\pm3.8$  ng/ml; t=2.56, df=34.6 [for unequal variances], p=.01). These groups, derived independently of information on amine levels (11), were compared in terms of mean levels of each of the aminergic system measures obtained, with age and sex covariates. Group 1 had markedly higher mean urinary epinephrine excretion than group 2 (p=.005, table 1) and higher urinary epinephrine excretion divided by creatinine excretion (F=10.80, df=1, 41, p=.002). Eleven of 15 (73%) of the hypersecreting, DST nonsuppressing depressed patients had epinephrine levels above the median for depressed patients, compared to nine of 30 (30%) of the depressed patients with urinary free cortisol normosecretion and DST suppression. Group 1, with clearly high HPA axis function, had significantly lower mean CSF levels of 5-HIAA (p=.005) and

TABLE 1. Urinary Epinephrine Excretion and CSF Levels of MHPG, 5-HIAA, and HVA in Depressed Patients With High and Normal HPA Function

	,	1	Urinary	Epinephr	ine			
	(1	Level 1g/24 ho	urs)	Analysis of Covariance <sup>a</sup>				
Patient Group	N	Mean	SD	F	df	p		
DST				2.75	1, 77	.10		
Nonsuppressors	29	26.9	14.6		-			
Suppressors	52	21.1	11.5					
Urinary free								
cortisol				13.88	1, 66	.0004		
Hypersecretors	31	28.1	13.5					
Normosecretors	39	17.0	9.9					
DST and urinary								
free cortisol				9.01	1, 41	.005		
Hypersecreting								
nonsuppressors	15	28.5	14.3					
Normosecreting								
suppressors	30	16.5	9.2					

<sup>&</sup>lt;sup>a</sup>Analyses of covariance covary for the effect of age and sex on amine or metabolite level. The analyses for epinephrine, MHPG, and 5-HIAA were run with logarithms of amine values, since the transformations removed significant deviations from normality of the distributions of raw values.

MHPG (p=.02). There were no significant differences in mean CSF levels of HVA (p=.19) or urinary excretion of norepinephrine, metanephrine, normetanephrine, MHPG, and VMA (p>.35 in all cases).

No strong relationship between HPA function and the amine levels measured in healthy control subjects was detected. There were few control subjects with elevated HPA function: eight of 77 were DST nonsuppressors, and five of 70 were urinary free cortisol hypersecretors. Seven of the eight DST nonsuppressors had measures of basal urinary free cortisol; only two were urinary free cortisol hypersecretors. None of the relationships between HPA function and amine measures listed in table 1 for depressed patients was statistically significant in healthy control subjects. Further, there was no significant correlation of urinary epinephrine (or CSF MHPG or 5-HIAA) with basal urinary free cortisol or postdexamethasone morning plasma cortisol in this group of healthy control subjects with relatively quiescent HPA activity.

#### DISCUSSION

These data reveal a clear relationship between indices of HPA system function and adrenomedullary activity in depressed patients. The simultaneous presence of cortisol hypersecretion and high urinary epinephrine excretion could reflect activation of the HPA axis by high levels of epinephrine, induction of epinephrine release by high cortisol levels at the adrenal medulla, or stimulation of adrenal epinephrine and cortisol secretion by a third factor, possibly CRH. While our data do not provide direct information regarding cause-and-effect relationships, it is of note

		CSF 1	MHPG					CSF	5-HIAA			CSF HVA					
	Level (pmol/ml)				Analysis of Covariance <sup>a</sup>			Level Analysis of (pmol/ml) Covariance <sup>a</sup>							nalysis c		
N	Mean	SD	F	dt	р	N	Mean	SD	F	df	p	N	Mean	SD	F	df	p
2 <i>5</i> 6 <i>5</i>	44.6 47.6	15.0 11.2	2.69	1, 86	.10	23 62	99.2 125	32.5 40.6	11.31	1, 81	.001	22 62	172 207	63.7 85.0	3.39	1, 80	.07
26 48	45.5 48.0	14.6 11.4	3.76	1, 70	.06	24 45	110 125	37.4 43.1	5.32	1, 65	.02	23 45	191 211	69.0 89.2	1.71	1, 64	.20
			6.10	1, 48	.02				8.68	1, 45	.005				1.80	1, 46	.19
12	40.6	15.0				11	96.2	39.0				11	177	69.9			
40	47.1	10.7				38	130	44.1				39	217	92.6			

that intracerebroventricular administration of CRH to the rat or dog produces increases in plasma epinephrine and norepinephrine (12). Some CRH-secreting cells impinge on central neurons of the sympathetic autonomic system (13) and also on the ventricular ependyma. There are recent reports of higher CRH concentrations in the CSF of depressed patients than in healthy control subjects (14). Epinephrine infused at physiological rates results in pituitary-adrenal activation in rats (3), possibly through  $\beta$ -adrenergic receptors on pituitary corticotropes (15) or by an effect on hypothalamic neurons secreting CRH (16). In addition, it has been reported that the ACTH release induced by insulin hypoglycemia can be inhibited by β-adrenergic blockade and most likely occurs because of a direct action of epinephrine on the pituitary (17). Previous analysis of results obtained from this same population of depressed patients suggests that overall, depressed patients as a group are characterized by a high production of catecholamines (4, 5).

In the aggregate, these results are compatible with the possibility that some depressed patients have a high release of CRH from CNS neurons, which then produces an activation of the sympathetic nervous system and adrenal medulla as well as the expected enhancement of HPA function, due to both the direct action of CRH and the possible subsequent action of epinephrine in releasing ACTH in humans. Alternatively, the initial event could be sympathoadrenomedullary release of epinephrine, resulting in subsequent activation of the pituitary-adrenocortical system. However, intravenous infusion of epinephrine to normal, healthy humans at rates producing clear metabolic and hemodynamic changes yielded no evidence of stimulation of the HPA axis (18).

Another possible explanation of our findings is that cortisol is known to induce the enzyme phenylethanolamine N-methyltransferase, which is the rate-limiting enzyme in the adrenomedullary transformation of norepinephrine to epinephrine (19). To invoke this explanation, it would be necessary to show that although the pressure of cortisol is necessary for normal basal phenylethanolamine N-methyltransferase activity, excessive cortisol concentrations in themselves produce hypersecretion of epinephrine. An increased phenylethanolamine N-methyltransferase activity induced by cortisol might be expected to increase the molar ratio of epinephrine to norepinephrine in urine. We noted a trend for urinary free cortisol hypersecretors to have higher epinephrine/norepinephrine ratios than normosecretors (19 of 31 hypersecretors and 13 of 33 normosecretors were above the median epinephrine/norepinephrine ratio in depressed patients;  $\chi^2$ = 3.06, df=1, p=.08). There was no significant correlation of urinary epinephrine/norepinephrine with urinary free cortisol (r=-.02 in these 64 patients).

Our data showing an association between high HPA activity and low CSF 5-HIAA levels are consistent with earlier observations in animals (20). We note that some investigators have found no major role for a serotonergic mechanism in the control of HPA activity (21). Even so, others have reported that serotonin inhibits the expected stress-induced increase in HPA activity (22), while others have found enhanced HPA function after administration of serotonin precursors to depressed patients (23) and rats (24). An inverse relationship between CSF levels of cortisol and 5-HIAA in depressed patients has been reported (25).

Barnes et al., in a study of nine depressed patients, found significantly higher plasma epinephrine and

norepinephrine levels in four DST nonsuppressors than in five suppressors (26). Rubin et al. reported that DST nonsuppressors had higher baseline plasma free MHPG than did the DST suppressors (27), and Rosenbaum et al. found a positive correlation between urinary MHPG and urinary free cortisol in depressed patients (28). The focus in those studies, as well as in a preliminary report from our group (29), was on MHPG as a marker for norepinephrine, although in fact it is a metabolite of both norepinephrine and epinephrine. We find that high HPA activity in depressed patients is associated with high adrenomedullary epinephrine excretion. Our data provide further description of how depressed patients with high versus normal HPA activity differ in levels of CSF and peripheral amines and provide potentially important leads for further understanding of the interactions between biogenic amine and HPA systems.

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#### REFERENCES

- Katz MM, Secunda SK, Hirschfeld RMA, et al: NIMH Clinical Research Branch Collaborative Study on the Psychobiology of Depression. Arch Gen Psychiatry 1979; 36:765-771
- 2. Maas JW, Koslow SH, Davis JM, et al: Biological component of the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression, I: Background and theoretical considerations. Psychol Med 1980; 10:759–776
- Tilders FJH, Berkenbosch F, Smelik PG: Adrenergic mechanisms involved in the control of pituitary-adrenal activity in the rat: β-adrenergic stimulatory mechanism. Endocrinology 1982; 110:114–120
- Koslow SH, Maas JW, Bowden CL, et al: CSF and urinary biogenic amines and metabolites in depression and mania: a controlled, univariate analysis. Arch Gen Psychiatry 1983; 40: 999–1010
- Davis JM, Gibbons RD, Maas JW, et al: Amine excretion in depressives and controls, in CME Syllabus and Scientific Proceedings in Summary Form, 136th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1983
- Mason JW: A review of psychoendocrine research on the pituitary-adrenal cortical system. Psychosom Med 1968; 30: 576-607
- Stokes PE: Studies on the control of adrenocortical function in depression, in Recent Advances in the Psychobiology of the Depressive Illnesses: DHEW Publication HSM 70-9053. Edited by Williams TA, Katz MM, Shield JA Jr. Washington, DC, US Government Printing Office, 1972
- 8. Carroll BJ, Feinberg M, Greden JF, et al: A specific laboratory test for the diagnosis of melancholia: standardization, valida-

- tion, and clinical utility. Arch Gen Psychiatry 1981; 38:15–22 9. Secunda S, Koslow SH, Redmond DE Jr, et al: Biological component of the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression, II: methodology and data analysis. Psychol Med 1980; 10:777–793
- Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
- 11. Stokes PE, Stoll PM, Koslow SH, et al: Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. Arch Gen Psychiatry 1984; 41:257–267
- 12. Brown MR, Fischer LA: Corticotropin releasing factor: effects on the autonomic nervous system and visceral systems. Fed Proc 1985; 44:243–248
- Palkovits M, Brownstein MJ, Vale W: Distribution of corticotropin-releasing factor in rat brain. Fed Proc 1985; 44 (1, part 2):215-219
- 14. Nemeroff CB, Widerlov E, Bissette, G, et al: Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 1984; 226:1342–1343
- Mezey E, Reisine TD, Palkowits M, et al: Direct stimulation of beta-2-adrenergic receptors in rat anterior pituitary induces the release of adrenocorticotropin in vivo. Proc Natl Acad Sci USA 1983; 21:6728–6731
- Vermes I, Berkenbosch F, Tilders FJH, et al: Hypothalamic deafferentation in the rat appears to discriminate between the anterior lobe and intermediate lobe response to stress. Neurosci Lett 1981; 27:89–93
- 17. Mezey E, Reisine TD, Brownstein MJ, et al: β-Adrenergic mechanism of insulin induced adrenocorticotropin release from the anterior pituitary. Science 1984; 226:1085–1086
- Clutter WE, Bier DM, Shah SD, et al: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest 1980; 66: 94–101
- 19. Wurtman RJ, Pohorecky LA, Baliga BS: Adrenocorticol control of the biosynthesis of epinephrine and proteins in the adrenal medulla. Pharmacol Rev 1972; 24:411-426
- Scapagnini U, Moberg GP, Van Loon GR, et al: Relation of brain 5-hydroxytryptamine content to the diurnal variation in plasma corticosterone in the rat. Neuroendocrinology 1971; 7: 90-96
- 21. Rotsztejn WH, Beaudet A, Roberge AG, et al: Role of brain serotonin in the circadian rhythm of corticosterone secretion in the corticotropic response to adrenalectomy in the rat. Neuroendocrinology 1977; 23:157–170
- Amar A, Mandal S, Sanyal AK: Effect of brain monoamines on the secretion of adrenocorticotrophic hormone. Acta Endocrinol 1982; 101:180–186
- 23. Meltzer HY, Lowy M, Robertson A: Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders, III: effect of antidepressants and lithium carbonate. Arch Gen Psychiatry 1984; 41:391–397
- 24. Fuller RW: Serotonergic stimulation of pituitary-adrenocortical function in rats, Neuroendocrinology 1981; 32:118–127
- Asberg M, Traskman L, Thoren P: 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry 1976; 33:1193--1197
- Barnes RF, Veith RC, Borson S, et al: High levels of plasma catecholamines in dexamethasone-resistant depressed patients. Am J Psychiatry 1983; 140:1623–1625
- Rubin AL, Price LH, Charney DS, et al: Noradrenergic function and the cortisol response to dexamethasone in depression. Psychiatry Res 1985; 15:5-15
- Rosenbaum AH, Maruta T, Schatzberg AF, et al: Toward a biochemical classification of depressive disorders, VII: urinary free cortisol and urinary MHPG in depressions. Am J Psychiatry 1983; 140:314–318
- Stokes PE, Frazer A, Casper R: Unexpected neuroendocrineneurotransmitter relationships. Psychopharmacol Bull 1981; 17:72-75

## CSF Corticotropin-Releasing Factor-Like Immunoreactivity in Depression and Schizophrenia

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To further investigate the hypothesis that hyperactivity of the hypothalamic-pituitary-adrenal axis in patients with depression may be mediated by hypersecretion of corticotropin-releasing factor (CRF), the authors measured CRF-like immunoreactivity in CSF samples from 138 neurological control, 54 depressed, and 27 nondepressed (23 schizophrenic and four manic) subjects. The CSF CRF concentration was markedly higher (almost twofold) in depressed patients than in control subjects and nondepressed psychiatric patients. The concentration of CSF CRF was slightly but significantly higher in schizophrenic patients than in control subjects. These findings provide further support for the hypothesis that CRF hypersecretion occurs in major depression.

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Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, one of the best established biological findings in depression (1, 2), has been demonstrated by such methods as measurement of urinary free and plasma cortisol and the dexamethasone suppression test (DST) (3–5). The regulation of HPA axis activity is, however, highly complex, involving multiple factors (6), and is incompletely understood. Plasma ACTH measurements after dexamethasone administration have produced somewhat inconsistent results (7, 8) but in general have indicated that postdexamethasone cortisol nonsuppression is associated with high plasma ACTH concentrations (9). The principal substance regulating pituitary ACTH release is believed to

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be corticotropin-releasing factor (CRF), a 41-amino acid peptide characterized and sequenced in 1981 by Vale and colleagues (10, 11) from ovine hypothalamus. Synthetic CRF has been available for human use for some time; Gold et al. (12) reported that depressed patients exhibited a blunted ACTH response to intravenously administered ovine CRF when compared to manic and recovered depressed patients or to control subjects. They interpreted these data as indicative of an intact cortisol feedback mechanism at the pituitary that halts the ACTH response to exogenous CRF because of the persistently high plasma cortisol concentrations. These researchers (13) also reported that prolonged CRF infusions (over 24 hours) in normal volunteers resulted in elevated plasma ACTH and cortisol concentrations, resembling the pattern observed in many depressed patients.

These observations, taken together, are compatible with the hypothesis that HPA hyperactivity in depression may be due, at least in part, to CRF hypersecretion. In addition, considerable preclinical literature now exists concerning the presence and role of CRF in extrahypothalamic brain areas (14). Direct CNS administration of CRF produces a variety of behavioral and physiological alterations that are reminiscent of the signs and symptoms of major depression. These include reduced food consumption, diminished sexual behavior, and alterations in locomotor activity (15-18). In a previous report from our laboratory (19), we reported a significantly higher mean concentration of CRF in the lumbar CSF of 23 patients with major depression than in normal control subjects and patients with schizophrenia or senile dementia.

In the present study, we measured the concentrations of CSF CRF-like immunoreactivity in a large group of psychiatric patients and neurological control subjects, using a standardized sampling procedure and DSM-III diagnoses.

#### **METHOD**

The neurological control group consisted of 138 hospitalized patients on a neurological unit at the Regional Neuropsychiatric Institute in Nagykallo, Hungary. This unit is primarily responsible for treating

chronic neurological diseases and also minor psychiatric disorders with or without any associated neurological illness. The control sample consisted of 65 men and 73 women with an age range of 18-68 years (mean  $\pm$ SD=43.2 $\pm$ 13.2 years for the men and 42.0 $\pm$ 12.9 years for the women; mean ±SD body weight=  $72.1\pm13.1$  kg for the men and  $63.7\pm11.5$  kg for the women), who had been hospitalized within 2 weeks for various peripheral neurological diseases such as neuralgias. Those with major CNS disease such as epilepsy, Parkinson's disease, or multiple sclerosis were not included. A detailed semi-structured interview, including a modified version of the Schedule for Affective Disorders and Schizophrenia (20), was conducted with each subject by a psychiatrist trained in using DSM-III diagnoses, to exclude the presence of any major psychiatric disorders in this group. The female control group included 13 subjects with adjustment disorder (with anxious or mixed emotional features), eight with somatization disorder, four with alcohol abuse, and seven with mild generalized anxiety disorder. The male control group included two individuals with anxiety disorder, four with adjustment disorder, and 27 with alcohol abuse.

The psychiatric patients were all women, except for one man with major depression from the neurological unit. They had all been recently hospitalized on one of the psychiatric wards of the same hospital; 54 patients  $(\text{mean} \pm \text{SD age} = 45.7 \pm 17.7 \text{ years; mean} \pm \text{SD body})$ weight=66.3±12.2 kg) fulfilled DSM-III criteria for major depression (17 of them also met criteria for melancholia and 26 for major depression with psychotic features), 23 patients fulfilled DSM-III criteria for schizophrenia (mean±SD age=39.8±11.4 years; mean ±SD body weight = 58.4 ± 11.4 kg), and four were in the manic phase of a bipolar disorder (mean± SD age=45.6±12.6 years; mean±SD body weight= 63.2±11.6 kg). Detailed physical examination and a laboratory test battery had been performed to exclude patients with any significant medical illness and to rule out pregnancy. Ratings on the Brief Psychiatric Rating Scale (BPRS) and on the Global Clinical Impression Scale (CGI) were obtained from all patients 1-3 days before the lumbar puncture, and all depressed patients were also rated on the 24-item Hamilton Rating Scale for Depression. Lumbar punctures were performed 4-7 days after hospital admission. None of the patients or control subjects had received antidepressants, neuroleptics, or anticonvulsants for at least 2 weeks or lithium for at least 6 months (1 year in the psychiatric patients). Except for 18 female control subjects who had recently received oral contraceptives (<50 mg of mestranol), none of the control subjects or psychiatric patients had received any steroid treatment.

After we obtained informed consent, lumbar punctures were performed in the morning (9:00 a.m.–10:00 a.m.) after an overnight fast and controlled bedrest. Two 6-ml portions of CSF were obtained at the fourth lumbar intervertebral space, and the first 6-ml fraction was used for peptide measurement. All CSF samples

were immediately placed on dry ice and then stored at  $-60^{\circ}$ C in the dark for no more than 4 months before the samples were transported, on dry ice and by air, to the United States for the CRF analysis. Samples were coded in Hungary; this code was not made available to the laboratory performing CRF measurements until all samples had been run. CRF-like immunoreactivity was determined by a sensitive and specific radio-immunoassay procedure as previously described (19), with an antiserum provided by Dr. Wylie Vale (Salk Institute, La Jolla, Calif.). All samples were measured in duplicate 400-µl aliquots of CSF in a single radio-immunoassay, and duplicate values varied less than 10%.

A DST was performed for all psychiatric patients on the evening after the lumbar punctures by administering 1 mg of dexamethasone orally at 10:00 p.m. and obtaining two blood samples for cortisol assay at 8:00 a.m. and 3:00 p.m. the next day. Cortisol was measured in plasma by a competitive protein-binding method with an intra-assay variance of 6% and an interassay variance of less than 12%.

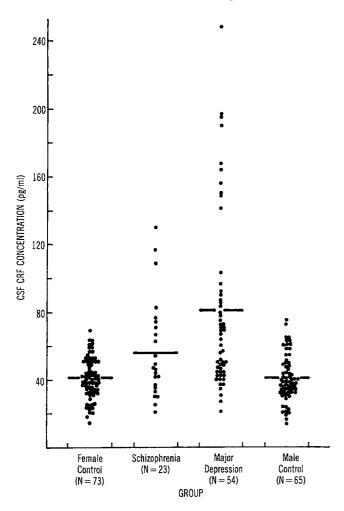
The statistical analysis of the data involved one-way analyses of variance, Newman-Keuls tests, t tests, chi-square analyses, and product-moment correlation coefficients (21).

#### RESULTS

The results of the measurement of CRF-like immunoreactivity in our patient groups are presented in figure 1. In the neurological control subjects, CSF CRF concentrations were normally distributed, and there was no difference between the CSF CRF concentrations for men and women (mean±SD=40.91±14.3 and 40.64±12.2 pg/ml, respectively). In addition, there were no significant differences in the mean CSF CRF concentrations among neurological patients with no psychiatric symptoms (40.84±12.2 pg/ml), alcohol abuse (38.60±16.1 pg/ml), generalized anxiety disorder ( $42.85\pm17.2$  pg/ml), adjustment disorder ( $41.68\pm$ 13.8 pg/ml), and somatization disorder (44.20±14.4 pg/ml) (F=0.38, df=4, 133). No correlation between CRF-like immunoreactivity and age (r=.06), body height (r=-.004), or body weight (r=.07) was found, in accordance with our previous findings concerning age and sex (19). When the mean CSF CRF concentration in the 18 female control subjects who had received oral contraceptives was compared to that in the female control subjects who were completely drugfree, no significant difference was found. In addition, there was no difference in CSF CRF concentrations between premenopausal and postmenopausal female control subjects. On the basis of these observations, we subsequently used the total neurological control sample as a uniform control group for comparison with the psychiatric patient groups.

The four manic patients (data not shown) had mean±SD CSF CRF levels almost identical to those of

FIGURE 1. CSF CRF-Like Immunoreactivity in Patients With DSM-III Schizophrenia, Patients With DSM-III Major Depression, and Control Subjects With Various Peripheral Neurological Diseases



the control subjects (42.90±15.87 pg/ml). On the other hand, the 23 schizophrenic patients showed a moderately but significantly higher mean±SD CSF CRF concentration than the control subjects (57.77±29.94 pg/ml) (t=4.57, df=159, p<.001). There was no significant difference in CSF CRF concentrations between first-admission and repeated-admission schizophrenic patients or among the various schizophrenic subtypes (five disorganized, eight catatonic, eight paranoid, and two undifferentiated).

Patients with DSM-III major depression exhibited a markedly higher (almost twofold) CSF CRF concentration than the control subjects (Newman-Keuls test, df=125, p<.001). The mean CSF CRF concentration in the depressed patents was also significantly higher than that of the schizophrenic group (Newman-Keuls test, df=94, p<.05). Six (26%) of the 23 schizophrenic patients and 24 (44%) of the 54 depressed patients had higher CSF CRF concentrations than the highest value among the sex-matched control subjects.

Although the neurological control group revealed normal distribution of CSF CRF levels, this was not the case for the depressed patients (figure 1). CSF CRF-like immunoreactivity in the patients strongly deviated from the normal distribution ( $\chi^2=31.35$ , df=5, p<.001). This finding suggests that in depression there is at least one subgroup with high CSF CRF values, and it resembles the situation observed with the DST in which, similarly, only 40%-60% of the patients exhibited cortisol nonsuppression (1, 5).

As in the control subjects, there was no correlation between the CSF CRF concentration and age, height, body weight, or body surface in the psychiatric patients. In addition, there was no correlation between the total Hamilton score and CSF CRF in the 54 depressed patients (r=.21), and there was no significant correlation between the CGI scores and CRF concentrations in the total psychiatric patient group (r=.09). We also performed an item-by-item correlation analysis on the full BPRS and CSF CRF concentrations separately in the depressed and the schizophrenic patient groups; only two correlation coefficients were found to be statistically significant (in schizophrenic patients only: r=.68 between delusions and CSF CRF; in depressed subjects only: r=.47 between somatic concern and CSF CRF), but the meaning of these findings must be considered doubtful because a large number of coefficients were calculated.

Nineteen of the 81 psychiatric patients attempted suicide shortly before the present hospitalization; there was no statistically significant association between the presence or absence of suicidal behavior and CSF CRF concentration in the CSF (22).

Twenty-one depressed patients, six schizophrenic patients, and one manic patient failed to suppress cortisol below 5  $\mu$ g/ml in both plasma samples after dexamethasone; the mean CSF CRF was  $81.65\pm59.7$  pg/ml in the nonsuppressors and  $68.12\pm54.0$  pg/ml in the suppressors, the difference being statistically not significant. Moreover, there was no significant correlation between the absolute postdexamethasone plasma cortisol values and the CSF CRF concentrations at either 8:00 a.m. (r=.07) or 3:00 p.m. (r=.06).

#### **DISCUSSION**

The present results confirm and extend earlier findings from this laboratory (19), namely, significantly higher CSF CRF concentrations in patients with DSM-III major depressive disorder than in schizophrenic patients or control subjects. The present psychiatric sample comprised recently hospitalized, severely ill subjects: 43 (80%) of the 54 depressed patients were either melancholic or psychotic, and all of the manic and schizophrenic patients exhibited florid psychotic symptoms at the time of the study.

Our previous (19, 23) and present studies show that high CSF CRF may not identify the same patients who are cortisol nonsuppressors; however, Gold et al. (personal communication) have recently found a significant correlation between postdexamethasone plasma cortisol and CSF CRF concentrations. It is likely that cortisol secretion involves more than regulation of secretion of ACTH. Moreover, CSF concentrations of CRF may not accurately reflect the concentrations of CRF that are present at the adenohypophyseal corticotroph. Immunoreactive CRF is present in several areas of the human brain outside the hypothalamus, including the thalamus, cerebral cortex, cerebellum, pons, medulla oblongata, and the spinal cord (24, 25), and little is known about the relative contribution of these areas to lumbar CSF CRF concentrations. While an abnormal DST may well involve CRF hypersecretion from nerve endings in the median eminence region of the hypothalamus, CRF release from other structures, e.g., the spinal cord, may obscure such changes of CRF secretion in higher brain centers when measured in lumbar CSF.

The higher CRF concentrations in depression were not attributable to differences in age, sex, body weight, or height between patients and control subjects; in accordance with our previous observations (19), these factors apparently are not major determinants of CSF CRF concentrations. In addition, there was no correlation between CSF CRF-like immunoreactivity and severity of depression or any of the specific symptoms assessed by the BPRS. It remains to be investigated whether high CSF CRF values are present only during the depressive episode or persist after recovery.

In contrast with our previous findings (19), we found higher mean CSF CRF concentrations in schizophrenic patients than in neurological control subjects. The higher mean value could be attributed largely to three individuals with CRF values greater than 100 pg/ml; unfortunately, we were unable to identify any clinical, biological, or demographic variable that might separate these subjects from the remainder of the group. Earlier we reported that catatonic and disorganized schizophrenic patients were more likely to be postdexamethasone cortisol nonsuppressors than were paranoid patients (26); two of the three schizophrenic patients with greater than 100 pg/ml of CSF CRF in the present study were of the paranoid subtype, and one was catatonic.

The relative specificity of the increase in CSF CRF concentration in depression is corroborated by the observation that neither alcohol abuse nor minor psychiatric disorders, such as somatization disorder, adjustment disorder, or generalized anxiety disorder, were associated with alterations in CSF CRF concentrations. Because recent alcohol abuse may alter DST results (27, 28), the CSF CRF-like immunoreactivity measurement appears to be more specific for depression.

In summary, the results derived from this relatively large patient sample are consistent with the hypothesis that CRF hypersecretion, as reflected by high concentrations in lumbar CSF, is present in about half of hospitalized patients suffering from major depression. Although moderately high CSF CRF concentrations may be found in some schizophrenic patients, alcohol

abuse and several minor psychiatric disorders are not associated with such CRF changes. Together with our earlier findings, these observations are concordant with the notion that the hypercorticolemia associated with major depression is, at least in part, due to a central hyperactivity of CRF neurons. However, little is known about the exact origin or nature of the immunoreactive CRF in lumbar CSF, and therefore its use as a functional index of hypothalamic CRF release is not yet validated.

#### REFERENCES

- Carroll BJ: The dexamethasone suppression test for melancholia. Br J Psychiatry 1982; 140:292–304
- Ettigi PG, Brown GM: Psychoneuroendocrinology of affective disorder: an overview. Am J Psychiatry 1977; 134:493–501
- 3. Kathol RG, Delahunt JW, Cooke R: Urinary free cortisol levels and dexamethasone suppression testing in organic affective disorder associated with hyperthyroidism. Am J Psychiatry 1985; 142:1193–1195
- Halbreich U, Asnis GM, Schindledecker R, et al: Cortisol secretion in endogenous depression. Arch Gen Psychiatry 1985; 42:904

  –908
- 5. Carroll BJ: Dexamethasone suppression test: a review of contemporary confusion. J Clin Psychiatry 1985; 46(2):13-24
- Proulx L, Giguere V, Cote J, et al: Multiple factors involved in the control of ACTH secretion. J Endocrinol Invest 1984; 7: 257-263
- Kalin NH, Weiler SJ, Shelton SE: Plasma ACTH and cortisol concentrations before and after dexamethasone. Psychiatry Res 1982; 7:87–92
- 8. Yerevanian BI, Woolf PD: Plasma ACTH levels in primary depression: relationship to the 24-hour dexamethasone suppression test. Psychiatry Res 1983; 9:45-51
- Herevanian BI, Woolf PD, Iker HP: Plasma ACTH levels in depression before and after recovery: relationship to the dexamethasone suppression test. Psychiatry Res 1983; 10:175-181
- Vale W, Spiess J, Rivier C, et al: Characterization of a 41 residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. Science 1981; 213:1394–1397
- Spiess J, Rivier J, Rivier C, et al: Determination of the primary structure of corticotropin-releasing factor from ovine hypothalamus. Proc Natl Acad Sci USA 1981; 78:6517-6522
- Gold PW, Chrousos G, Kellner C, et al: Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. Am J Psychiatry 1984; 141:619–627
- Gold PW, Chrousos GP: Clinical studies with corticotropinreleasing factor: implications for the diagnosis and pathophysiology of depression, Cushing's disease and adrenal insufficiency. Psychoneuroendocrinology 1985; 10:401-419
- 14. Kilts CD, Bissette G, Krishnan KRR, et al: The preclinical and clinical neurobiology of corticotropin-releasing factor, in Hormones and Depression. Edited by Halbreich U, Rose RM. New York, Raven Press (in press)
- Britton DR, Koob GF, Rivier J, et al: Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. Life Sci 1982; 31:363–367
- Levine AS, Rogers B, Kneip J, et al: Effect of centrally administered corticotropin-releasing factor (CRF) on multiple feeding paradigms. Neuropharmacology 1983; 22:337–339
- 17. Siringthsenghji DJS, Rees LH, Rivier J, et al: Corticotropin-releasing factor is a potent inhibitor of sexual receptivity in the female rat. Nature 1983; 305:232-235
- 18. Koob GF, Bloom FE: Corticotropin-releasing factor and behavior. Fed Proc 1985; 44:259-263
- Nemeroff CB, Widerlöv E, Bissette G, et al: Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 1984; 226:1342–1344
- 20. Endicott J, Spitzer R: A diagnostic interview: The Schedule for

- Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 3S:837-844
- Snedecor GW, Cochran WG: Statistical Methods, 7th ed. Ames, Iowa State University Press, 1980
- Banki CM, Arato M, Nemeroff CB, et al: Neuroendocrine and neurotransmitter changes in suicidal behavior, in Biological Psychiatry 1985. Edited by Shagass C. Amsterdam, Elsevier, 1986
- Bissette G, Spielman F, Stanley M, et al: Further studies of corticotropin-releasing factor-like immunoreactivity in CSF of patients with affective disorders. Society for Neuroscience Abstracts 1985; 11:133
- 24. Suda T, Tomori N, Tozawa F, et al: Distribution and characterization of immunoreactive corticotropin-releasing factor in

- human tissues. J Clin Endocrinol Metab 1984; 59:861-867
- Bissette G, Reynolds GP, Kilts CD, et al: Corticotropin-releasing factor-like immunoreactivity in senile dementia of the Alzheimer type: reduced cortical and striatal concentrations. JAMA 1985; 254:3067–3069
- Banki CM, Arato M, Rihmer Z: Neuroendocrine differences among subtypes of schizophrenic disorder? Neuropsychobiology 1984; 11:174–177
- Dackis CA, Bailey J, Pottash ALC, et al: Specificity of the DST and the TRH test for major depression in alcoholics. Am J Psychiatry 1984; 141:680-683
- Del Porto JA, Monteiro MG, Laranjeira RR, et al: Reversal of abnormal dexamethasone suppression test in alcoholics abstinent for four weeks. Biol Psychiatry 1985; 20:1156-1160

# Impact of Psychiatric Comorbidity on Length of Hospital Stay for Medical/Surgical Patients: A Preliminary Report

George Fulop, M.D., James J. Strain, M.D., Joseph Vita, B.S., John S. Lyons, Ph.D., and Jeffrey S. Hammer, M.D.

The impact of psychiatric comorbidity on the length of hospital stay was addressed in a study of all medical/surgical patients discharged in 1984 from the Mount Sinai Hospital in New York City (N=37,370) and Northwestern Memorial Hospital in Chicago (N=21,889). At both hospitals the mean±SD length of stay of the patients with psychiatric comorbidity was significantly longer than that of the other patients: 19.8±33.3 versus 9.2±15.3 days at Mount Sinai Hospital and 13.7±27.7 versus 8.3±13.2 days at Northwestern Memorial Hospital. Early identification of patients with psychiatric comorbidity would permit appropriate psychosocial intervention, which might shorten their hospital stays.

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In this era of cost containment, concurrent medical and psychiatric disorders—psychiatric comorbidity—assume increased importance. Due to the rapid escalation in medical costs, public policy now emphasizes limiting resource consumption by decreasing the length of stay of hospitalized medical/surgical patients. Coincidentally, there is an increased awareness of the psychosocial concomitants of physical disability and of the potential cost effectiveness of psychosocial interventions for the medically ill (1). Mumford et al. (2) and Lyons et al. (3) noted that the mean hospital stay of patients who received psychological intervention was 1–2 days less than that of control subjects. Consequently, it is essential to document the impact of psychiatric comorbidity on the patients' length of hospital stay.

As early as 1941, Billings (4) observed that the

average length of stay was 28 days among patients with psychiatric comorbidity but only 15 days among such patients who received rapid diagnosis and subsequent involvement of the psychiatric liaison service when indicated. In a study of discharge abstracts from short-term general hospitals with and without psychiatric units between 1970 and 1977, patients with psychiatric disorders diagnosed according to the hospital adaptation of *ICDA* (H-ICDA-2) (5) stayed an average of 10.8 days, whereas the mean stay of all patients (including the patients with psychiatric comorbidity) was 7.3 days (6).

This study directly compared the length of hospital stay of medical and surgical patients with psychiatric comorbidity who were not transferred to a specialized psychiatric unit to the length of stay of patients without psychiatric comorbidity.

#### **METHOD**

The discharge abstracts of all medical and surgical patients hospitalized in 1984 at Mount Sinai Hospital in New York City (N=37,370) and from Northwestern Memorial Hospital in Chicago (N=21,889) were reviewed. Only those patients whose principal diagnoses were medical or surgical were included. Patients on the medical/psychiatric units were excluded.

The data at Mount Sinai Hospital were collected on the Utilization Information Service hospital discharge abstract form (7). This database includes length of stay, demographic data, and diagnoses, which include an admitting diagnosis, a retrospectively determined principal diagnosis for the condition that resulted in the admission, and up to six secondary diagnoses. The psychiatric diagnoses on the abstracts were made by psychiatric consultants (18%) and primary physicians (82%).

Four clinical data reviewers, all professional nurses, confirmed all diagnoses in a 10–15-minute review of each chart; there was 95% agreement between the nurses and the chief rater (based on quarterly samples of 25 charts) (8). An external audit of the discharge abstracting procedure revealed an overall potential 4.2% error rate in coding diagnosis-related groups (DRGs) (8). Additional data collected involved admis-

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TABLE 1. Length of Stay for All Medical/Surgical Patients and for Medicare Beneficiaries With and Without Psychiatric Comorbidity at Two Hospitals

	Number of		Len	gth of Sta	y (days)	Compari	Comparison of Length of Stayb			
Group	Patients	Mean	SD	Range	Geometric Mean <sup>a</sup>	t	df	p		
All medical/surgical inpatients										
Mount Sinai Hospital						14.1	37,368	.0001°		
Psychiatric comorbidity	2,009	19.8	33.3	1-791	10.7		,			
No psychiatric comorbidity	35,361	9.2	15.3	1-738	5.4					
Northwestern Memorial Hospital	ŕ					10.8	21,887	.0001°		
Psychiatric comorbidity	811	13.7	27.7	1-88	8.7		,			
No psychiatric comorbidity	21,078	8.3	13.2	1-43	5.2					
Medicare beneficiaries										
Mount Sinai Hospital						9.1	10,028	.0001°		
Psychiatric comorbidity	969	24.3	33.6	1-508	14.1		,			
No psychiatric comorbidity	9,061	14.2	20.0	1-529	8.3					
Northwestern Memorial Hospital						6.9	8,009	.001°		
Psychiatric comorbidity	416	15.3	26.8	1-87	10.1		•			
No psychiatric comorbidity	7,595	10.4	12.8	1-45	6.9					

<sup>&</sup>lt;sup>a</sup>The geometric mean reduces skewing of the sample distribution and may be a less biased estimator of central tendency.

sion, hospital course, and discharge characteristics. The data at Northwestern Memorial Hospital were obtained from the hospital discharge summary abstract and included only demographic data at admission, diagnoses, and length of stay.

All inpatients were divided according to the presence or absence of psychiatric comorbidity. Psychiatric comorbidity was defined as any of ICD-9-CM/DSM-III psychiatric diagnosis codes 290–319 in any secondary diagnostic entry. The average length of stay and geometric mean length of stay were derived for both groups. (The geometric mean length of stay represents the central tendency for a distribution of whole number integers. Given that number of days in the hospital meets this criterion, the geometric mean may be a less biased estimate of the population central tendency and also serves to decrease the skewedness of the geometric distribution [9].) We also determined the length of stay for the Medicare beneficiaries with and without psychiatric comorbidity.

Statistical significance was assessed with two-tailed t tests assuming unequal subsample variance for all continuous variables and chi-square analysis for polychotomous items, with an overall .05 significance level. The Bonferroni procedure was used to control the error rate in testing multiple hypotheses (10).

#### RESULTS

The patients with psychiatric comorbidity in both Mount Sinai Hospital and Northwestern Memorial Hospital stayed significantly longer than the groups without psychiatric comorbidity (table 1.) The geometric mean length of stay was also greater for the patients with psychiatric comorbidity. All subsequent data presented will be for the Mount Sinai Hospital sample only.

#### Patient Characteristics

Age, sex, and race are shown in table 2. The patients with psychiatric comorbidity were significantly older, and those in the overall sample were less likely to be female; the Medicare patients revealed no significant difference for sex. The groups with psychiatric comorbidity had significantly more black and Hispanic inpatients.

Examination of the admission, hospital course, and discharge characteristics revealed that significantly more of the medical/surgical patients with psychiatric comorbidity had been admitted in emergency situations (49.0% versus 23.0%;  $\chi^2 = 725$ , df=1, p<.001) and from other health care facilities (5.8% versus 1.1%;  $\chi^2$  = 339, df = 1, p<.001). Their hospital courses were characterized by significantly more consultations  $(\text{mean} \pm \text{SD} = 1.4 \pm 1.6 \text{ versus } 0.5 \pm 1.0; t = 26.3, df =$ 37,368, p<.001), operative procedures (mean  $\pm$ SD=  $2.4\pm1.8$  versus  $2.0\pm1.5$ ; t=11.1, df=37,368, p< .001), and medical diagnoses (mean  $\pm$ SD=3.8 $\pm$ 1.7 versus  $3.0\pm1.8$ ; t=21.1, df=37,368, p<.0001). Finally, the medical/surgical patients with psychiatric comorbidity were significantly more likely to die  $(8.0\% \text{ versus } 3.3\%; \chi^2 = 125, \text{ df} = 1, p < .0001) \text{ or to be}$ discharged to a long-term care facility (10.5% versus 1.5%;  $\chi^2 = 774$ , df=1, p<.001). To account for testing of multiple hypotheses (N=20), a p value of <.0025(Bonferroni procedure) was regarded as significant.

#### Medical and Psychiatric Diagnoses

Among the five most prevalent DRG categories for the Medicare inpatients, the average length of stay was generally higher in the group with psychiatric comorbidity but did not achieve statistical significance with the Bonferroni procedure (i.e., p < .01). The mean  $\pm$  SD length of stay of the patients with and without psychi-

bSignificance assessed with two-tailed t test assuming unequal subsample variance.

cSignificant at overall .05 level (Bonferroni procedure p value of <.0125).

TABLE 2. Demographic Characteristics of All Medical/Surgical Inpatients and of Medicare Beneficiaries With and Without Psychiatric Comorbidity at Mount Sinai Hospital

		Psychiatric	Comorbidity				
	Pres	ent	Abse	ent	Chi-Square Analysis		
Characteristic <sup>a</sup>	N	%	N	%	χ²	df	_p
All medical/surgical inpatients	2,009	5.4	35,361	94.6			
Female	1,039	51.7	21,358	60.4	61:0	1	.0001 <sup>b</sup>
Race	•		,		134.0	3	.0001 <sup>b</sup>
White	1,153	57.4	21,888	61.9			
Black	404	20.1	4,668	13.2			
Hispanic	398	19.8	6,224	17.6			
Other	54	2.7	2,581	7.3			
Medicare beneficiaries	969	9.6	9,061	90.4			
Female	529	54.6	4,802	53.0	0.9	1	.35
Race			•		9.7	3	.02 <sup>b</sup>
White	714	73.7	6,959	76.8			
Black	131	13.5	979	10.8			
Hispanic	107	11.0	906	10.0			
Other	17	1.8	217	2.4			

<sup>&</sup>lt;sup>a</sup>The mean±SD ages of the medical/surgical patients with and without psychiatric comorbidity were 55.4±23.0 and 41.6±26.0 years, respectively (t=26.0, df=37,368, p=.0001<sup>b</sup>). For the Medicare beneficiaries the ages of the two groups were 73.8±14.0 and 71.8±11.0 years (t=4.35, df=10,028, p=.001<sup>b</sup>).

bSignificant according to a Bonferroni adjusted p value of .02 for the medical/surgical and Medicare samples.

TABLE 3. Psychiatric Diagnoses and Associated Length of Stay for 2,009 Medical/Surgical Inpatients With Psychiatric Comorbidity at Mount Sinai Hospital

	Patients Wi	th Diagnosis <sup>b</sup>	Length of Stay (days)					
Psychiatric Disorder <sup>a</sup>	N	%	Mean	SD	Range	Geometric Mean		
Organic mental disorder								
DSM-III section 1								
Dementia	39	1.9	29.7	41.3	1-173	14.8		
Substance-induced organic mental disorder	132	6.6	17.3	35.4	1-366	8.5		
DSM-III section 2—organic mental disorder								
secondary to physiologic process	483	24.0	23.6	33.4	1-508	14.5		
Substance use	561	30.5	13.1	17.3	1-264	7.6		
Affective disorder	366	18.2	26.9	33.6	1-273	15.2		
Other disorder	193	9.6	18.2	59.5	1-791	7.6		
Psychosis	180	9.0	23.3	33.0	1-314	13.5		
Anxiety	146	7.3	14.5	15.7	1-88	8.6		
Adjustment disorder	75	3.7	27.8	27.7	1-172	17.6		
Personality disorder	61	3.0	16.4	23.0	1-150	9.2		

<sup>&</sup>lt;sup>a</sup>Determined by ICD-9/DSM-III codes.

atric comorbidity, respectively, was  $6.8\pm6.5$  and  $3.2\pm2.7$  days for DRG 39 (lens procedure) (t=2.2, df=495, p<.05) and  $20.6\pm17.9$  and  $12.5\pm10.5$  days for DRG 127 (heart failure) (t=2.4, df=264, p<.02).

Eight ICD-9/DSM-III categories and the associated length of stay of the medical/surgical inpatients are presented in table 3. The organic mental disorders accounted for 27.1% of the psychiatric diagnoses and were predominantly substance induced or secondary to physiologic processes and not dementias arising in the senium and presenium. Substance use and affective disorders were also prevalent.

The overall rates of psychiatric consultation among all patients and those with Medicare insurance were 1.9% (N=697) and 3.2% (N=317), respectively. Among the outliers (patients whose hospital stays were greater than two standard deviations above the Medicare mean length of stay, 8.5% (N=305) received psychiatric consultations.

There were significantly more outliers among the patients with psychiatric comorbidity than among the other patients; in the medical/surgical sample, outliers accounted for 24.3% (N=489) and 8.7% (N=3,079), respectively ( $\chi^2$ =538, df=1, p=.001), and in the Medicare sample they accounted for 31.5% (N=489) and 16.4% (N=1,486) ( $\chi^2$ =136, df=1, p=.001) (chisquare analysis with Bonferroni protected p value of .0025).

<sup>&</sup>lt;sup>b</sup>Each patient may have had more than one *DSM-III* category of psychiatric diagnoses. The 2,009 medical/surgical patients with psychiatric comorbidity had a mean±SD of 1.2±0.5 psychiatric diagnoses.

#### **DISCUSSION**

Since a greater mean length of stay and geometric mean length of stay were found for patients with psychiatric comorbidity on general hospital wards at two different university hospitals, the results are unlikely to be an idiosyncratic characteristic of either site. Within several DRG categories, the presence of a psychiatric diagnosis was associated with a longer mean length of stay. This extended hospital stay among patients with psychiatric comorbidity may be secondary to more severe medical illnesses, the additional diagnostic and treatment required by the psychiatric disorders, or psychopathology that confounds the treatment and management of the medical disorders.

Caution must be exercised in the interpretation of the study findings. First, whereas estimates of psychiatric comorbidity in medical/surgical inpatients range up to 30%-50% (11), the rate of detection of psychiatric disorders in this study was 5%. Second, even though an independent study of the abstraction process found a low rate of diagnosis coding errors (8), the reliability and validity of the nonpsychiatrist's descriptions and the medical record abstractor's coding of the psychiatric disorders remain an issue. Although only 18% of the patients receiving psychiatric diagnoses had psychiatric consultations, this is similar to the 11.5% rate found in a national probability sample of all patients in short-term general hospitals (12).

Third, the difference between the groups with and without psychiatric comorbidity in admission, hospital course, and discharge variables were not covaried in the current analysis. These variables would be suitable control variables in prospective hypothesis-testing studies. Fourth, the notably higher rate of psychiatric consultation among the outliers suggests an alternative hypothesis—the longer one stays in the hospital, the more likely it is that a psychiatric disorder will manifest itself, be detected, or engender negative feelings in physicians that lead them to call for a psychiatric consultation. This may increase the rate of diagnosis of psychiatric disorders among longer-stay patients.

Fifth, the timing of the psychiatric consultations in the study sample was not evaluated. The timing of psychiatric consultation has been correlated with length of stay by Lyons et al. (3)—the later the consultation, the longer the hospital stay. Finally, what constitutes a psychiatric disorder in a medically ill person is debatable. For example, one can argue that delirium really indicates an aberrant physiological process—a medical illness and therefore not a psychiatric disorder. However, delirium traditionally has been recorded as a major psychiatric disorder, as indicated in DSM-III. An intriguing clinical question remains: Why did the patients with psychiatric diagnoses appear more ill, i.e., have significantly more emergency admissions, consultations, and operative procedures and have a greater likelihood of dying or being discharged to long-term care facilities?

#### Implications for Public Policy and Patient Care

Despite these considerations, to our knowledge this is the largest contemporary sample of medical/surgical inpatients studied with the ICD-9/DSM-III diagnostic criteria in which an association between longer length of stay and psychiatric comorbidity was found. This longer length of stay has implications for public policy and patient care. For instance, although each DRG was designed to represent a homogeneous group of inpatients, who make equal use of hospital resources, considerable variability within DRGs has been observed (13, 14). Preliminary examination of DRGs in this study suggests a greater length of stay with psychiatric comorbidity patients than among medical/ surgical patients without psychiatric diagnoses. The relative insensitivity of DRGs to issues complicating individual cases, e.g., comorbidity or severity of illness, has been documented by others (13, 14).

The current DRG reimbursement mechanism provides incentives for treatment plans that are focused but not generalized or comprehensive, thereby creating a disincentive for measures aimed at the primary or secondary detection of psychiatric comorbidity in the medically ill. Even though many psychiatric disorders experienced during medical hospitalizations are transient (15), once detected the mental disorders are undertreated and unlikely to receive appropriate psychiatric treatment after hospitalization; it has been reported (16, 17) that only 4%–34% receive appropriate treatment. Furthermore, the lack of detection of psychiatric disorders not only endangers psychiatric aftercare but threatens compliance with the prescribed medical regimen (18, 19).

If it is discerned that psychiatric detection and intervention result in savings, then strategies for fiscal incentives for the identification and treatment of psychiatric disorders should be undertaken through the DRG system. Perhaps the transfer of select patients with psychiatric comorbidity to psychiatric/medical units not regulated by DRGs would promote the treatment of psychiatric disorders discovered on medical units (20). This would facilitate appropriate psychiatric disposition and protect against the uncertreatment of psychiatric morbidity. Premature hospital discharge of patients with psychiatric comorbidity because of the length of stay constraints imposed by DRG fiscal incentives may also be prevented.

However, specialized treatment units, as well as all psychiatric units, may soon lose their prospective payment system exemption, removing this fiscal option. In fact, Fogel et al. (20) reported that under DRGs, specialized medical/psychiatric units (primarily medical) fared worse financially than the DRG-exempt psychiatric/medical units (primarily psychiatric). Unless special considerations for psychiatric comorbidity are included in a new DRG reimbursement formula, treatment of patients with psychiatric comorbidity will likely result in deficits for hospitals (20).

To definitively substantiate the study findings, more

complex and comprehensive studies are required and are forthcoming. Necessary future studies include: 1) cross-sectional epidemiological surveys of psychiatric comorbidity in the hospitalized medically/surgically ill, 2) prospective studies examining all medical/surgical inpatients at admission and discharge for the presence of psychiatric disorders and determining the associated length of stay, 3) multivariate model building to assess the effect of independent variables (e.g., psychiatric comorbidity, psychosocial characteristics, demography, and severity of medical and psychiatric illness) on length of stay, 4) studies of the cost effectiveness of psychosocial intervention with regard to length of stay, and 5) the effect of DRGs on the detection and/or treatment of psychiatric comorbidity. Such studies may elucidate the mechanism underlying the role of psychiatric comorbidity in extending length of stay and have major policy implications for early identification and treatment of psychiatric comorbidity in the medical setting.

#### REFERENCES

- Levitan J, Kornfeld DS: Clinical and cost benefits of liaison psychiatry. Am J Psychiatry 1981; 138:790-793
- Mumford E, Schlesinger HJ, Glass GV: The effects of psychological intervention on recovery from surgery and heart attacks: an analysis of the literature. Am J Public Health 1982; 72:141–151
- Lyons JS, Hammer JS, Strain JJ, et al: The timing of psychiatric consultation in the general hospital and length of hospital stay. Gen Hosp Psychiatry 1986; 8:159-162
- 4. Billings EG: Value of psychiatry to the general hospital. Hospitals 1941; 15:305–310
- Hospital Adaptation of ICDA, 2nd ed (H-ICDA-2). Ann Arbor, Mich, Commission on Professional and Hospital Activities,

1973

- Wallen J: Use of Short-term General Hospitals by Patients with Psychiatric Diagnoses—Hospital and Cost Utilization Project Research Note 8: DHHS Publication PHS 86-3395. Washington, DC, US Government Printing Office, 1985
- Utilization Information Service. Albany, NY, Hospital Association of New York State, 1983
- 8. Data Quality Assessment Report. Albany, NY, Hospital Association of New York State, 1986
- Hays W: Statistics, 3rd ed. New York, Holt, Rinehart & Winston, 1981
- Grove MA, Andreasen NC: Simultaneous tests of many hypotheses in exploratory research. J Nerv Ment Dis 1982; 170:3–8
- Lipowski ZJ: Review of consultation psychiatry and psychosomatic medicine, II: Clinical aspects. Psychosom Med 1967; 29: 201–224
- 12. Wallen J, Pincus HA, Goldman HH, et al: Psychiatric consultations in short-term general hospitals. Arch Gen Psychiatry 1987; 44:163–168
- Horn SD, Bulkley G, Sharkey PD, et al: Interhospital differences in severity of illness: problems for prospective payment based on diagnosis-related groups (DRGs). N Engl J Med 1985; 313: 20-24
- Berki SE, Ashcraft ML, Newbrander WC: Length-of-stay variations within ICDA-8 diagnosis-related groups. Med Care 1984; 22:126–142
- 15. Sensky T: Failure to keep psychiatric follow-up appointments (letter). Gen Hosp Psychiatry 1985; 7:272–273
- Karasu RB, Plutchik R, Steinmuller RI, et al: Patterns of psychiatric consultation in a general hospital. Hosp Community Psychiatry 1977; 28:343-347
- Burstein A: Psychiatric consultations in a general hospital: compliance with follow-up. Gen Hosp Psychiatry 1984; 6:139– 141
- 18. Stam M, Strain JJ: Refusal of treatment: the role of psychiatric consultation. Mt Sinai J Med (NY) 1985; 52:4-9
- Strain JJ: Noncompliance, in Psychological Interventions in Medical Practice. New York, Appleton-Century-Crofts, 1978
- Fogel BS, Stoudemire A, Houpt JL: Contrasting models for combined medical and psychiatric inpatient treatment. Am J Psychiatry 1985; 142:1085-1089

# Estimated Distribution of Effort by Providers of Mental Health Services to U.S. Adults in 1982 and 1983

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A national sample of psychiatrists, psychologists, social workers, and primary care physicians responded to a survey of their professional activities. From these data, the authors estimate that during a representative 60-day period, 6.7% of U.S. adults visited one of these types of professionals for a mental or emotional condition. All four groups spent the largest portion of their time with nonpsychotic patients. Most patients with schizophrenia, mania, or major depression were treated by psychiatrists. Services from primary care physicians were usually provided in the context of a concurrent physical condition. Psychologists and social workers tended to treat the less severe mental and emotional conditions.

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omponents of the U.S. Department of Health and Human Services have periodically contracted for surveys of the use of health services by the civilian noninstitutionalized population of the United States. The National Medical Care Expenditure Survey, conducted in 1977, found that about 5% of the population had one or more ambulatory care visits for a mental or emotional condition in 1977 (1). Moreover, although 60% of all users received services only from the general medical sector (e.g., primary care physicians), 66% of all visits were to mental health specialists. Using data from the 1973 and 1975 National Ambulatory Medical Care surveys of private officebased physicians, Regier and his colleagues showed that most persons with mental and emotional conditions received relevant services from the general medical sector (2). The National Ambulatory Medical Care survey data for 1980 and 1982 confirmed these findings but provided evidence that visit-intensive treatment for serious and persistent mental and emotional conditions was provided primarily by mental health specialists (3).

Apportionment of patients' visits among the various mental health specialists has also been a focus of more recent research. Taube and colleagues, using data from the 1980 National Medical Care Utilization and Expenditure Survey, reported that psychiatrists and psychologists in office-based practice each accounted for between 27 and 28 million visits by 48% of the 9.5 million people who had one or more visits for ambulatory mental health care in 1980 (4). The 1982 Membership Data Bank Survey of the National Association of Social Workers (NASW) identified mental health as the largest area of practice for social workers, occupying the majority of work time for 26.6% of the members (5).

These data have greatly extended our knowledge of mental health services. Because patients' visits are a coarse measure of providers' work, however, the data can provide only limited information about the distribution of providers' effort. For example, 100 visits could be made by from one to 100 patients. Moreover, data on visits alone fail to describe the nature or seriousness of the patient's condition or the apportionment of time across conditions. This article attempts to address these questions by examining the differing distribution of working hours by psychiatrists, psychologists, social workers, and primary care physicians across practice settings and groups of patients for a representative workweek between May 1982 and August 1983. Additional contrasts are made in terms of the average and total number of patients seen for various categories of conditions during a representative 60-day period during the same months. These data help to quantify the various contributions from these professionals, to identify where their efforts overlap, and to suggest where each group's activities are unique.

#### **METHOD**

This report draws on data from the Mental Health Service Providers Survey, which we have described extensively elsewhere (6). Briefly, representative national samples of psychiatric and primary care physicians were drawn from the American Medical Associ-

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ation's (AMA's) and the American Osteopathic Association's physician masterfiles, samples of psychologists from the National Register of Health Service Providers in Psychology (7), and samples of social workers from the National Association of Social Workers' NASW Register of Clinical Social Workers (8). Beginning in May 1982 and ending in August 1983, all of these groups received similar mailed questionnaires that had been extensively pretested. Different cohorts received their instrument during different months of the survey period to avoid seasonal bias. Sampling frames were progressively updated over the course of the survey. Of 9,073 eligible respondents, 5,958 (65.7%) returned usable questionnaires.

Practitioners were asked to describe all adult (age 18 and over) patients treated and hours worked during the 60-day period immediately preceding receipt of the questionnaire, in terms of patients for whom they alone were primarily responsible. A 60-day period allowed for representation of patients seen infrequently for the management of medication or prevention of relapse. Also, these procedures minimized the possibility of patients' receiving services from more than one provider.

The questionnaires presented and briefly defined six clusters of diagnoses or problems that are considered to represent similar conditions. The clustering method has been shown to be an effective tool for comparing groups of physicians engaged in different professional practices (9). The clusters of conditions paralleled the major categories in *DSM-III*. Two exceptions were made because pretesting suggested strongly that all providers treated a large number of patients who did not have a condition attributable to a mental disorder, a finding that has found further support in our own work as well as that of others (6, 10, 11). To capture data about these patients, the general terms "neurosis" and "relationship problems" were added.

The term "neurosis" is still commonly used in clinical practice and was defined to include only patients with mild depressive neurosis (i.e., dysthymia) or a neurotic process. "Relationship problems," which comprise most of DSM-III's V codes (i.e., conditions not attributable to a mental disorder that are a focus of attention or treatment), were defined as problems with marriage, family, job, peers, school, or community and other similar situations.

Patients whose problems did not fit into any of the clusters were given a designation of "other." Specifically excluded from this category and all clusters were obesity, migraine headache, irritable colon, and similar conditions that are often affected by emotions but are not generally considered mental problems or disorders per se. Adjustment disorders were omitted because pretesting and an unpublished concurrent study indicated that respondents tended to include this condition with relationship problems, neuroses, or "other."

Several concurrent studies were conducted to verify the reliability of our data. One (12) found that selfreports about the number of patients seen and visits provided closely approximated the "objective" data found in patients' records. In a related study (13), the diagnostic assessment abilities of psychiatrists, psychologists, and social workers were found to be comparable across diagnosis clusters similar to those used in the present study. These two studies and a related study of nonresponse bias (6) suggested that the Mental Health Service Providers Survey data used in this report accurately described the aggregate professional activities of mental health service providers belonging to professional associations.

The overall response rate to the survey's request for aggregate patient counts was only 55% of the 5,958 respondents. This rate varied considerably among professional groups: for psychiatrists, the item response rate was 59% (N=969); for psychologists, 80% (N=1,404); for social workers, 77% (N=779); and for primary care physicians, 26% (N=128). Thus, the findings, particularly for primary care physicians, must be considered as somewhat tentative. An analysis of nonresponse bias in which the methods we have described (6) were used revealed that the sample was representative of the professions, even for primary care physicians, suggesting that it was the burden of responding to the survey rather than professional attributes which accounted for the differences in response bias.

The means in this report are estimates derived by multiplying the number of responses by the inverse of the probability of the respondents' being selected for inclusion in the sample. The variance of the estimates was calculated according to the method described by Raj (14).

To make our calculations, it was necessary to estimate the total number of active psychiatrists, psychologists, social workers, and primary care physicians comparable to our respondents in the 50 states and the District of Columbia who might have been expected to treat individuals with mental or emotional conditions in 1983. Accordingly, mental health service providers were counted only if they had completed training, were clinically active in the mental health field, and were members of or eligible for membership in the American Psychiatric Association, the American Psychological Association, the NASW, the AMA, or the American Osteopathic Association.

Reasonably accurate counts of the groups of physicians are available from published sources issued by the AMA (15) and the National Center for Health Statistics (16). These counts include members as well as nonmembers of the AMA and the American Osteopathic Association. Of the estimated 20,700 osteopathic physicians in 1983 (16), approximately 118,423 (89.0%) were primary care physicians (17). Using these sources, we estimated that 28,729 adult and child psychiatrists and 116,642 primary care physicians (doctors of medicine or osteopathy) were clinically active in 1983 in the 50 states and the District of Columbia.

A count of doctoral-level clinical psychologists in

TABLE 1. Characteristics of U.S. Mental Health Service Providers' Workweek

	Psychiatrists		Psyc	hologists	Socia	l Workers	Primary C	Care Physicians
Characteristic	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>
Total hours worked per week Direct treatment <sup>b</sup> hours	47.5	0.2	41.4	0.1	37.3	0.2	52.8	0.3
per week								
All settings <sup>c</sup>	33.1	0.4	23.6	0.2	20.6	0.2	12.2	1.1
Private practice	22.4	0.4	18.1	0.2	11.8	0.2	8.9	0.9
Public practice	7.9	0.2	3.0	0.1	5.0	0.1	2.2	0.6
Medical school	2.0	0.04	0.4	0.01	0.6	0.02	0.4	0.03
Other settings	1.1	0.02	2.1	0.04	3.3	0.1	0.4	0.03
Percentage of total hours working with selected clusters of patients								
Inpatients Schizophrenia, mania,	19.0	3.2	7.2	0.6	7.9	1.04	10.7	2.3
and major depression	27.7	1.8	8.0	0.1	9.5	0.3	1.5	0.1
Neurosis, anxiety, and personality disorders Relationship	33.4	1.4	37.6	0.5	31.8	0.6	7.0	1.3
problems <sup>d</sup>	9.6	0.1	20.6	0.1	21.1	0.3	4.8	0.6

<sup>a</sup>See reference 14 for the method used for calculating variance.

b"Direct treatment" means a series of face-to-face professional contacts with a patient for the primary purpose of eliminating or changing the severity of a mental or emotional disorder or of preventing or slowing further deterioration.

<sup>d</sup>Problems with marriage, family, job, peers, school, or community and similar situations.

1983 was one result of a census conducted by the American Psychological Association. This census counted 44,580 doctoral-level clinical psychologists who provided (or administered) health and mental health services in 1983 (18).

The number of social workers providing mental health services in 1983 was estimated as follows. In 1985 an estimated 97,000 social workers belonged to NASW, and 100,000 did not belong; thus, the ratio of nonmember to member social workers was 1.03. In 1982 there were 90,476 NASW members (5), and, assuming a constant nonmember-to-member ratio, 93,190 (90,476 $\times$ 1.03) social workers who were not NASW members, or a total of 183,666 trained social workers. NASW's 1982 Membership Data Bank Survey found that 29.5% of the members were primarily involved in providing services to individuals with either mental (26.6%) or alcohol, drug, or substance abuse (2.9%) problems (5). Again assuming constant percentages, 29.5% of 183,666, or 54,181, social workers provided mental health services in 1982. Assuming a 1.3% growth per year (5), approximately 54,883 trained social workers worked in the mental health field in 1983.

#### RESULTS

Table 1 shows that on the average, primary care physicians worked the greatest number of hours per week (about 53) and social workers the fewest (about

37). Primary care physicians spent about 12 hours per week providing services to patients with mental or emotional problems—about one-half of the time spent by psychologists and social workers and about one-third of the time spent by psychiatrists.

The representative practitioner provided mental health services in more than one setting. The private office or hospital practice was favored by all groups. Psychiatrists spent about 46% of their total workweek in private practice; psychologists and social workers, about 32%. For psychiatrists and psychologists, public practice (i.e., state, public, and federal hospitals and community mental health centers and associated facilities) was clearly less favored. In contrast, social workers spent about 30% of their workweek with patients in the public sector. Table 1 also shows that all providers devoted the largest portion of their time to individuals with neurosis, personality or anxiety disorder, and/or relationship problems. Psychiatrists spent about 28% of their time treating individuals with schizophrenia, mania, or major depression, which probably accounts for the finding that psychiatrists spent a larger percentage of time (19%) working with inpatients than did other providers (7%-11%). It should be noted that some of these figures are associated with large estimates of variance.

Table 2 presents the mean number of patients in each cluster of diagnoses seen by a typical provider over a representative 60-day period during 1982–1983. The most striking finding was the large number of patients treated for mental and emotional condi-

Practice settings were aggregated as follows: medical school included university hospitals; private practice included solo and group private practice and private general and mental hospitals; public practice included state, public, and federal general and mental hospitals and community mental health centers and associated facilities.

TABLE 2. Patients Seen by Mental Health Service Providers During the Previous 60 Days for Selected Clusters of Conditions

	Each I	nts Seen by Psychiatrist Respondents)	Each F	nts Seen by Psychologist 04 Respondents)	Each So	nts Seen by ocial Worker Respondents)	Patients Seen by Each Primary Care Physician (126–128 Respondents)		
Cluster of Conditions	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>	Mean	Variance <sup>a</sup>	
Schizophrenia, mania,									
and major depression	35.4	6.2	4.1	0.1	5.5	0.2	4.4	0.4	
Substance abuse and									
alcoholism	7.0	0.4	2.5	0.05	2.6	0.1	9.2	2.2	
Somatoform and									
psychosexual disorders	5.4	1.2	2.4	0.5	1.2	0.01	6.7	0.7	
Neurosis, anxiety, and									
personality disorders	19.8	3.0	14.0	0.2	11.6	0.2	12.9	8.6	
Relationship problems <sup>b</sup>	5.7	0.2	7.7	0.05	8.1	0.1	8.8	2.4	
Other conditions	4.9	0.3	2.3	0.1	2.1	0.1	10.4	2.4	
All clusters	78.1	26.4	32.9	1.0	31.2	1.0	52.2	32.1	

<sup>&</sup>lt;sup>a</sup>See reference 14 for the method used for calculating variance.

TABLE 3. Estimates of U.S. Adults Receiving Care From Mental Health Service Providers for Selected Clusters of Conditions During an Average 60-Day Period in 1982 or 1983

Cluster of	Adults S by 28,7 Psychiati	29	Adults S by 44,5 Psycholog	80	Adults S by 54,8 Social Wo	83	Adults Seen by Primary Care F		Adults See the Total of 2 Provide	244,834
Conditions	N	%	N	%	N	%	N	%	N	%
Schizophrenia, mania, and major depression Substance abuse and	1,017,581	50.3	184,115	9.1	303,503	15.0	519,057	25.6	2,024,256	100.0
alcoholism	199,954	13.1	111,450	7.3	143,793	9.4	1,071,940	70.2	1,527,137	100.0
Somatoform and psychosexual disorders Neurosis, anxiety, and	155,424	14.0	106,546	9.6	65,311	5.9	781,501	70.5	1,108,782	100.0
personality disorders	567,398	17.0	622,783	18.6	639,387	19.2	1,509,347	45.2	3,338,915	100.0
Relationship problems <sup>a</sup>	162,893	8.2	341,482	17.3	444,003	22.5	1,027,616	52.0	1,975,994	100.0
Other conditions	140,772	9.0	102,534	6.5	115,803	7.4	1,214,243	77.2	1,573,352	100.1
Total	2,244,022	19.4	1,468,910	12.7	1,711,800	14.8	6,123,704	53.0	11,548,436	99.9

<sup>&</sup>lt;sup>a</sup>Problems with marriage, family, job, peers, school, or community and similar situations.

tions by primary care physicians. Each primary care physician treated almost as many patients (52 patients) with these conditions as psychologists and social workers combined. The psychiatrists treated 78 patients, or about 26 more patients than any other provider.

Primary care physicians indicated that one-fourth of their patients with mental and emotional conditions received services for their mental condition only and three-fourths for a physical condition as well. Thus, while the primary care physician may treat a substantial number of emotionally impaired patients, services are more frequently provided in the context of a concurrent physical condition. Primary care physicians also provided more services to patients with substance use, somatoform, psychosexual, and "other" disorders than did the other groups of providers. For primary care physicians, the "other" cluster may have contained mostly patients with organic brain syndromes (unpublished data).

Table 3 gives the estimated total numbers of adults

receiving care in the United States from each of four mental health service provider groups over a 60-day period. According to these estimates, which were made by multiplying the supply of providers by the mean number of patients in each cluster of conditions (table 2), approximately 11.5 million adults (6.7% of the U.S. population) were receiving mental health services from the groups of providers we studied. Of these patients, approximately 53% were receiving services from primary care physicians, 19% from psychiatrists, 15% from social workers, and 13% from psychologists. The vast majority of the 2 million patients with schizophrenia, mania, or major depression were treated by physicians (psychiatrists, 50%; primary care physicians, 26%), whereas most nonpsychotic patients received mental health services from nonpsychiatrists. While physicians in general appeared to treat the most heterogeneous mixture of conditions, related studies indicated that psychiatrists saw the more impaired patients for longer and at more frequent intervals (1, 4, 6).

<sup>&</sup>lt;sup>b</sup>Problems with marriage, family, job, peers, school, or community and similar situations.

#### DISCUSSION

The results of this study cannot be easily compared with those of earlier studies such as the 1973-1974 study of private practice psychiatry (19), because the percentage of psychiatrists (and presumably of other providers) working part-time in a variety of organized care settings has increased substantially over the last decade or so (20). Volume of patients per unit of time is generally higher in these settings (21). Therefore, the present study found that providers were seeing more patients than might otherwise be assumed. Moreover, results were affected by the reporting period. "The last typical workweek," for example, underrepresents patients seen at infrequent intervals (22). Our survey asked about a 60-day period, which allowed for better representation of patients seen infrequently for the management of medication or prevention of relapse.

The 60-day utilization figures permit rough estimates of treated *period* prevalence rates. For example, 5.8%—the National Institute of Mental Health Epidemiologic Catchment Area Program's minimum estimated prevalence rate for substance use disorders (23)—multiplied by the 171.5 million U.S. residents who were 18 years of age or older in 1983 (24) yields 10 million people with this condition. Table 3, however, suggests that only about 1.5 million people (15%) received treatment from the four groups of providers we studied. Similar calculations showed that although treated prevalence rates varied by cluster of diagnoses, all rates fell below 50%.

Unlike previous studies, this study considered all mental and emotional conditions treated by psychiatrists, psychologists, social workers, and primary care physicians. A major but unsurprising finding was that all these groups provided services to all types of patients. The most impressive overlap among providers occurred for patients with neurotic, personality, or anxiety disorders and for conditions not attributable to a mental disorder (i.e., those in the DSM-III V codes). When effort was measured in terms of percentage of work time, patients with these conditions appeared to receive a substantial amount of provider effort. Indeed, the bulk of the efforts of psychologists and social workers went to these groups. The majority of psychiatrists' patients, by contrast, had diagnoses of schizophrenia, mania, major depression, substance abuse, and alcoholism. Primary care physicians had substantial numbers of patients in all of the categories considered and distributed their work time fairly evenly across these categories.

These providers appeared to spend much of their time treating conditions that many people would consider minor. Our findings tend to support the belief that persons with primarily "psychological" problems receive labor-intensive treatment, whereas persons with problems most often associated with biological components tend to have relatively infrequent contact with a professional. It is important to recognize, however, that there are serious doubts that increased

professional attention to the severely disabled has much long-term impact on clinical outcome (25, 26).

Because of the number of primary care physicians, their contributions to the care of the mentally and emotionally impaired are substantial (1–3). Present measurements of this contribution may be misleading, however, because much of the primary care physician's mental health work may be in assessment, brief treatment, and referral of difficult cases to other professionals (3, 6, 27). Also, the contributions by psychologists and social workers are underestimated because of data limitations. Nondoctoral-level psychologists were excluded from our counts, and an unknown number of social workers working in fields other than mental health are likely to provide some mental health services. Of course, other groups (clergy, counselors, etc.) provide these services as well.

Given that all providers of mental health services tend to see some groups of patients that are similar, the impact of increases in the numbers of these providers must be considered. The ranks of psychologists and social workers have swelled dramatically in recent years (5, 18, 28). These two groups of providers probably continue to concentrate their efforts on the less severe mental and emotional conditions. If this trend continues, consumers of mental health services may be progressively drawn away from physicians who provide similar services. Changing ratios among the groups of providers may thus force each group to market its most specialized skills and contribute to an increasing distinction in the nature of their services. Although competitive pressure disrupts present patterns of practice, it may be of considerable long-term benefit to consumers seeking mental health care.

#### REFERENCES

- Horgan CM: Specialty and general ambulatory mental health services. Arch Gen Psychiatry 1985; 42:565–572
- Regier DA, Goldberg ID, Taube CA: The de facto US mental health services system: a public health perspective. Arch Gen Psychiatry 1978; 35:685-693
- 3. Schurman RA, Kramer PD, Mitchell JB: The hidden mental health network: treatment of mental illness by nonpsychiatrist physicians. Arch Gen Psychiatry 1985; 42:89–94
- Taube CA, Burns BJ, Kessler L: Patients of psychiatrists and psychologists in office-based practice. Am Psychol 1980; 39: 1435–1447
- Membership survey shows practice shifts. NASW News, Nov 1983, pp 6-7
- Knesper DJ, Pagnucco DJ, Wheeler JRC: Similarities and differences across mental health services providers and practice settings in the United States. Am Psychol 1985; 40:1352–1369
- National Register of Health Service Providers in Psychology. Washington, DC, Council for the National Register of Health Service Providers in Psychology, 1982
- NASW Register of Clinical Social Workers. Silver Spring, Md, National Association of Social Workers, 1982
- Schneeweiss R, Rosenblatt RA, Cherkin DC, et al: Diagnosis clusters: a new tool for analyzing the content of ambulatory care. Med Care 1983; 21:105-122
- Shapiro S, Skinner EA, Kessler LG, et al: Utilization of health and mental health services. Arch Gen Psychiatry 1984; 41:971– 978
- 11. Leaf PJ, Livingston MM, Tischler GL: Contact with health

#### DISTRIBUTION OF EFFORT

- professionals for the treatment of psychiatric and emotional problems. Medical Care 1985; 23:1322-1337
- Knesper DJ, Pagnucco DJ: Accuracy of provider-supplied human resources data. Am Psychol 1984; 39:1485–1486
- Knesper DJ, Pagnucco DJ, Kalter NM: Agreement on patient diagnosis, treatment, and referral across provider groups. Professional Psychology 1986; 17:331–337
- Raj D: Sampling Theory. New York, McGraw-Hill, 1968, pp 62-84
- Eiler MA: Physician Characteristics and Distribution in the United States. Chicago, American Medical Association, 1984
- Health United States, 1984: Department of Health and Human Services Publication PHS 85-1232. Hyattsville, Md, National Center for Health Statistics, Dec 1984
- 17. McDevitt FJ (chairman): Preliminary Draft Report of the Task Force on Graduate Osteopathic Medical Education. Chicago, American Osteopathic Association, 1980, p 26
- Stapp J, Tucker AM, VandenBos GR: Census of psychological personnel: 1983. Am Psychol 1985; 40:1317–1351
- Marmor J, Scheidemandel PL, Kanno CK: Psychiatrists and Their Patients: A National Study of Private Office Practice. Washington, DC, Joint Information Service of the American Psychiatric Association and the National Association for Mental Health, 1975

- 20. Fenton WS, Leaf PJ, Moran NL, et al: Trends in psychiatric practice, 1965-1980. Am J Psychiatry 1984; 141:346-351
- Koran LM, Taintor Z, Mirza M: Patient characteristics and treatment modalities, in The Nation's Psychiatrists: 1982 Survey. Edited by Koran LM. Washington, DC, American Psychiatric Association, 1987
- 22. Albee GW: Into the valley of therapy rode the six thousand. Contemporary Psychology 1976; 21:525-527
- 23. Myers JK, Weissman MM, Tischler GL, et al: Six-month prevalence of psychiatric disorders in three communities. Arch Gen Psychiatry 1984; 41:959–967
- Statistical Abstract of the United States, 1985, 105th ed. Washington, DC, Bureau of the Census, Dec 1984
- Gunderson JG, Frank AF, Katz HM, et al: Effects of psychotherapy in schizophrenia, II: comparative outcome of two forms of treatment. Schizophr Bull 1984; 10:564

  –598
- McGlashan TH: The Chestnut Lodge follow-up study, II: long-term outcome of schizophrenia and affective disorders. Arch Gen Psychiatry 1984; 41:586–601
- Orleans CT, George LK, Houpt JL, et al: How primary care physicians treat psychiatric disorders: a national survey of family practitioners. Am J Psychiatry 1985; 142:52–57
- Goldman D: Social workers vault into a leading role in psychotherapy. New York Times, April 30, 1985, pp 17, 20

# Characteristics of Very Poor Outcome Schizophrenia

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The authors compared 21 "Kraepelinian" schizophrenic patients who had been ill and dependent on others for the past 5 years with 76 chronic schizophrenic patients in remission or with exacerbations requiring hospitalization. The Kraepelinian patients met the criteria for schizophrenia by more diagnostic systems than the exacerbated patients, were less responsive to haloperidol, had more severe negative symptoms, and had similarly severe positive symptoms. They had cerebral ventricles that were more asymmetrical and a greater family history of schizophrenia spectrum disorders than the other chronic patients. These data suggest that patients with 5 years of illness and complete dependency on others may represent a subgroup of schizophrenia.

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hronic, unremitting schizophrenia places a greater demand on the health care system than any other psychiatric illness. Financially, close to 30% of the total economic expense of mental illness and addictive states in 1983 was attributed to patients with schizophrenia, despite their representing less than 5% of the psychiatrically treated population (1). Obviously, the most chronically deteriorated patients, who require either continuous hospitalization or continuous care, demand the most attention from social and financial resources and are most in need of study. Noninvasive, descriptive measures associated with chronicity would be of value in identifying and classifying those patients who will eventually reach this severely deteriorated state. To date, psychiatry lacks

the pathological, biochemical, or etiological evidence used by other branches of medicine to validate systems of classification and therefore depends on other types of validating criteria. The areas frequently investigated for purposes of validating classification in psychiatry include outcome, clinical description, biology, exclusion criteria, and family study (2). If cross-sectional noninvasive measures in these areas could discriminate chronically deteriorated schizophrenic patients from those less deteriorated chronic schizophrenic patients whose longitudinal course includes periods of total or partial remission, initial steps toward identifying an important subgroup of schizophrenia would be taken.

This study compared a group of severely deteriorated schizophrenic male veterans, who for the past 5 years had been either continuously hospitalized or unable to provide themselves with necessities such as food, shelter, and clothing, to a group of chronic schizophrenic male veterans, whose prior longitudinal course included periods of total or partial remission alternating with exacerbations requiring inpatient care. It should be noted that both groups consisted of relatively low functioning individuals. In view of the similarity between the longitudinal course of the severely deteriorated schizophrenic patients and the progressive deterioration of dementia praecox described by Kraepelin (3), these patients were designated "Kraepelinian" schizophrenic patients. Cross-sectional characteristics of both groups were obtained by the following noninvasive techniques: diagnostic and clinical interviews, ventricular measurement, treatment response study, and family interview for ascertainment of a family history of schizophrenia or other disorders in the schizophrenic spectrum (4). The severely deteriorated Kraepelinian patients, if they were distinguishable from other chronic schizophrenic patients, may differ by diagnostic measures, such as the frequency of diagnosis of schizophrenia according to various diagnostic criteria (5–7), as well as by descriptive measures associated with poor prognosis, such as absence of response to neuroleptic treatment, time in hospital, age at onset, and level of functioning. In addition, data suggest that ventricular abnormalities (8, 9), negative symptoms (10-12), absence of an affective syndrome (13, 14), and family history of schizophrenia spectrum disorders (14) may be other potential indicators of poor prognosis Kraepelinian schizophrenia.

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#### **METHOD**

Subjects

The sample consisted of 97 male chronic schizophrenic patients ranging in age from 22 to 65 years  $(\text{mean} \pm \text{SD} = 38.1 \pm 11.1)$  admitted to the Schizophrenia Biological Research Center of the Bronx Veterans Administration (VA) Medical Center and Mount Sinai School of Medicine. All patients met criteria for definite schizophrenia or schizoaffective disorder, mainly schizophrenic, according to the Research Diagnostic Criteria (RDC) (15) and/or definite schizophrenia according to the Feighner diagnostic system (16). Patients were separated into three clinical groups: stable, exacerbated, and Kraepelinian. Stable patients (N=15) were all volunteers, who by definition were not in need of hospitalization for the 3 months before admission, and received four weekly scores on the Brief Psychiatric Rating Scale (BPRS) (17), with a range of less than 10 points (mean  $\pm$  SD = 30.0  $\pm$  6.0). The most severely deteriorated patients, the Kraepelinian group (N=21), met the following criteria for the past 5 years: 1) either continuous hospitalization or, if living outside the hospital, complete dependence on others for necessities such as food, shelter, and clothing; 2) no useful work or employment; and 3) no evidence of a remission of symptoms. Patients in the exacerbated group (N=61)required hospitalization but did not meet the criteria for the Kraepelinian group.

Informed consent was obtained from the patient or from a first-degree relative if an otherwise assenting patient was unable to give true informed consent.

#### Diagnosis and Clinical Description

All patients were interviewed by a two-member diagnostic team that used the Schedule for Affective Disorders and Schizophrenia (SADS) (18). Team members independently determined diagnoses according to the following criteria: RDC and the Feighner system, which were used as entrance criteria for the study; DSM-III; the "flexible" system of the International Pilot Study of Schizophrenia (19), which uses criteria derived from a discriminant function analysis of symptoms of patients given a clinical diagnosis of schizophrenia; Schneiderian first-rank symptoms (20), which are strictly positive symptoms; Langfeldt criteria (21), which are purported to be indicators of poor prognosis; and the ICD-9 system (22). The RDC were used to determine if in addition to schizophrenic symptoms, a patient had ever manifested a full affective syndrome, defined as a prominent mood disturbance accompanied by at least four significant affective symptoms.

Kappa values for the interrater reliabilities for these criteria were as follows: *DSM-III*, 0.88; RDC, 0.90; Feighner system, 0.91; International Pilot Study of Schizophrenia—five symptoms required for diagnosis, 0.80, and six symptoms, 0.64; Schneiderian symptoms, 0.65; Langfeldt criteria, 0.59; and *ICD-9*, 0.80.

Severity of formal thought disorder was measured by the Thought, Language and Communication Scale (23). Current social and occupational functioning was measured with the Level of Functioning Scale (24). Negative symptoms were assessed in 54 patients by determining total scores (excluding global and subjective rating scores) on the Scale for the Assessment of Negative Symptoms (25). In addition, because these scores were not determined for each patient, negative symptoms severity scores (26) were assessed for the entire cohort by using items on the SADS; Thought, Language and Communication Scale; and Level of Functioning Scale that corresponded to 16 of the 30 items on the Scale for the Assessment of Negative Symptoms. Total scores for negative symptoms severity and the Scale for the Assessment of Negative Symptoms were found to be highly correlated (r=.73)in patients for whom both scores were available. Positive symptom severity scores (26) were determined by summing SADS items rating severity of hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Premorbid sexual functioning was assessed by the sociosexual adjustment item of the Premorbid Asocial Adjustment Scale (27), the only item reported to have adequate interinformant reliability in an earlier study that used a subgroup of the present cohort (28).

Data regarding age at onset, number of psychiatric hospitalizations, total time in psychiatric hospitals, and educational level were gathered for all patients. In nearly all cases, the two best informants available were interviewed and all medical records were reviewed in order to verify and supplement information gathered by the patient interview. Consensus scores and diagnoses were determined for all diagnostic and descriptive data by both team members and an independent diagnostic expert, who resolved any disagreements.

Diagnostic family histories were gathered on 87 patients by a specialist in family diagnostic interviews who was blind to whether the patient was Kraepelinian. In 50 cases, two family members were interviewed; in the other 37 cases, one family member was interviewed. A family history of schizophrenia spectrum disorders was defined as any first- or seconddegree relative who met the criteria for any of the following Family History RDC (29) definite or probable diagnoses: chronic schizophrenia; schizoaffective disorder, chronic type; or unspecified functional psychosis, chronic type. Diagnosis of definite or probable schizophrenia-related personality (4) was also used as a criterion for a family history of schizophrenia spectrum disorders. The morbid risk of schizophrenia spectrum disorders was calculated for all first-degree relatives of each patient to correct for the size of the patient's family. The Weinberg-abridged method was used to correct for an otherwise likely underestimation of risk due to the possibility that relatives who had not fully passed through the age of risk (defined as ages 15-39 for schizophrenia spectrum disorders) may yet manifest a disorder.

#### Treatment Response

Thirty exacerbated chronic schizophrenic patients and 17 Kraepelinian patients underwent a standardized dose schedule of haloperidol to determine treatment response. All patients received 10 mg of haloperidol b.i.d. for 28 days. When clinically indicated, haloperidol dose was increased to 15 mg b.i.d. until day 36, at which time it was increased to 20 mg b.i.d. until day 43. Treatment response was assessed by means of BPRS and Clinical Global Impression (CGI) scores, which were obtained weekly by two independent raters. Baseline BPRS score was determined by calculating the means of four scores acquired over a 2-week drug-free period before haloperidol administration.

#### Ventricle-Brain Ratio

Seventy-two schizophrenic patients underwent CAT scans on a high-resolution Technicon 2020 scanner to determine the ventricle-brain ratio (VBR). The slices scanned were 1 cm apart, parallel to the orbitomeatal line. The cut that displayed the lateral ventricles most prominently was used to determine the VBR. The ventricular margins were outlined by means of an operator-controlled joystick, with the enclosed area automatically displayed, for the individual right and left lateral ventricles. Similarly, the area of the brain on that slice was also determined. The averages of the left and right lateral ventricular areas were summed and divided by the brain areas, and the result was multiplied by 100 to yield the VBR for that rater. Each VBR was determined by two separate raters, who were blind to the age and diagnosis of the subject. The final VBRs used in subsequent analyses were the numerical averages of these two raters' measurements. Intrarater reliability was high (ICC=.99) for both raters, and interrater reliability was also strong (ICC=.96). These outlines were photographed and reviewed later by a neuroradiologist to ensure that the lateral ventricles were correctly identified.

In addition to the VBR, a separate measure of ventricular symmetry was calculated. The mean area of the left ventricle for each rater was divided by the mean area of the right ventricle, resulting in the left-to-right lateral ventricular ratio for each rater. The mean of this ratio for both raters was used in subsequent calculations.

#### **RESULTS**

Consensus diagnoses for all patients reflected several important differences among patients in the Kraepelinian and exacerbated groups (see table 1). Overall, Kraepelinian patients were diagnosed as having schizophrenia by a mean of 6.4 of the seven diagnostic systems, while exacerbated patients met the criteria for schizophrenia by 5.6 of them (t=-3.70, df=72.13,

TABLE 1. Positive Diagnosis of Schizophrenia by Seven Diagnostic Systems in Kraepelinian (Most Severely Deteriorated) and Exacerbated Schizophrenic Patients

	Positive Diagnosis of Schizophrenia							
Diagnostic		pelinian s (N=21)	Exacerbated Patients (N=61)					
System	N	%	N	%				
RDC <sup>a</sup>	20	95 <sup>b</sup>	47	77				
DSM-III <sup>c</sup>	21	100	56	92				
International Pilot Study of Schizophrenia								
5	21	100 <sup>d</sup>	45	74				
6	19	90 <sup>e</sup>	38	62				
Feighner criteria <sup>f</sup>	18	86 <sup>g</sup>	<b>3</b> 3	54				
Langfeldt criteria	19	90	57	93				
Schneiderian first								
rank symptoms	16	76	46	75				
ICD-9	21	100	60	98				

<sup>&</sup>lt;sup>a</sup>Fourteen exacerbated patients were given a diagnosis of schizo-affective disorder.

p<.001). Kraepelinian and exacerbated patients were most widely discrepant in meeting the criteria for diagnostic systems that either exclude patients for having an affective syndrome or use the absence of affective symptoms as an inclusion criteria for a diagnosis of schizophrenia. Specifically, fewer Kraepelinian patients had an affective syndrome. Fourteen of the 61 exacerbated patients were given an RDC diagnosis of schizoaffective disorder, mainly schizophrenic, compared with only one of the Kraepelinian patients (p=.05, Fisher's exact test).

There was a trend for Kraepelinian patients to have more severe formal thought disorder, as measured by the Thought, Language and Communication Scale (mean  $\pm$ SD scores = 14.6  $\pm$ 6.6 versus 10.9  $\pm$ 7.6; t= -1.93, df=80, p<.06). Positive symptoms, as determined by the positive symptom severity score from SADS items and by numbers of Schneiderian and Langfeldt symptoms, revealed no significant differences between the two groups (p>.10 for all measures, t test). Among the 54 patients for whom total scores on the Scale for the Assessment of Negative Symptoms were determined, Kraepelinian patients had slightly higher total scores, but this difference was not significant (mean  $\pm$  SD = 48.0  $\pm$  13.2 versus 41.0  $\pm$  16.9; t= -1.36, df=52, p<.20). Negative symptoms severity scores, available for the entire cohort, demonstrated significant differences between Kraepelinian and exacerbated patients (mean  $\pm$ SD=38.5 $\pm$ 11.0 versus 30.5 $\pm$ 11.8; t=2.71, df=80, p<.01).

As expected, Kraepelinian patients differed from exacerbated patients on several other measures. They

<sup>&</sup>lt;sup>b</sup>p<.10 (Fisher's exact test for all comparisons).

<sup>&</sup>lt;sup>c</sup>Five exacerbated patients were given a diagnosis of schizoaffective disorder.

 $<sup>^{</sup>d}p < .005.$ 

 $<sup>^{</sup>e}p < .05$ .

<sup>&</sup>lt;sup>f</sup>Twelve exacerbated patients were given a diagnosis of "probable" schizophrenia.

gp<.01.

TABLE 2. Significant Differences Between Kraepelinian (Most Severely Deteriorated) and Exacerbated Schizophrenic Patients

Variable		an Patients =21)	Exacerbate (N=			df	р
	Mean	SD	Mean	SD	t		
Age (years) Months in hospital	46.7 120.9	11.2 108.7	36.0 35.5	10.8 54.9	3.83 4.34	80 70	<.001 <.001
Levels of Functioning Scale score	14.5	2.8	21.3	6.1	4.90	80	<.001

TABLE 3. Family History of Schizophrenia and Morbid Risk in First-Degree Relatives for Kraepelinian (Most Severely Deteriorated) and Non-Kraepelinian Schizophrenic Patients

Item	Kraepelinian Patients (N=18)	Non-Kraepelinian Patients (N=69)
Family history of schizophrenia in first- and second-degree relatives <sup>a</sup>		
Yes	11	24
No	7	45
First-degree relatives		
Number age 15-39 years	23	149
Number age 40 years		
or older	61	196
Lifetimes of risk	72.5	270.5
Cases of schizophrenia		
spectrum disorder	14	29
Morbid risk <sup>b</sup>	0.193	0.107

<sup>&</sup>lt;sup>a</sup>χ<sup>2</sup>=4.11, df=1, p<.05. <sup>b</sup>Z=1.94, df=1, p=.05.

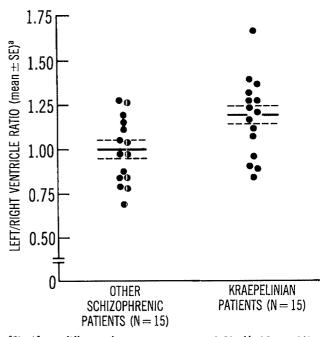
had worse social and occupational functioning as measured by the Level of Functioning Scale, they had spent more time in psychiatric hospitals, and they were older (p<.01 for all measures; t test; see table 2). Kraepelinian patients did not differ significantly from exacerbated schizophrenic patients on measures of age at onset (25.7 versus 24.4 years), education (11.3 versus 12.1 years), premorbid sexual functioning as measured by the Premorbid Asocial Adjustment Scale (score of 3.3 for each group), number of hospitalizations (7.4 versus 5.6), and VBR (6.4 versus 6.0) (p>.05 for all measures, t test).

Kraepelinian patients had significantly more cases of schizophrenia spectrum disorders in their first- and second-degree relatives than did the non-Kraepelinian patients, and their first-degree relatives had a higher morbid risk of schizophrenia spectrum disorders than did the first-degree relatives of the other patients (see table 3).

Response to haloperidol was defined as 1) a decrease in BPRS scores of at least 20% from baseline to either day 29 or the last day of the study or 2) a two-point decrease in CGI scores from baseline to either day 29 or the last day of the study. None of the 17 Kraepelinian patients responded to haloperidol treatment; however, 13 of the 30 exacerbated patients did respond (p<.001, Fisher's exact test).

Because of the possible effects of age on ventricular measures, the Kraepelinian schizophrenic patients were compared to a group of age-matched chronic

FIGURE 1. Ventricular Asymmetry in Kraepelinian (Most Severely Deteriorated) and Other Chronic Schizophrenic Patients Matched by Age



<sup>a</sup>Significant difference between groups (t=-2.53, df=28, p<.02).

schizophrenic patients. There was a significant difference between the two groups in ventricular asymmetry. The mean±SD left/right ventricle ratio was 1.17±0.22 for the Kraepelinian group (N=15) versus 0.99±0.18 for the group of other chronic schizophrenic patients (N=15) (see figure 1). All but two of the patients in this cohort were right-handed. In our preliminary study of 60 patients, handedness showed no relationship to ventricular asymmetry. No significant difference was found in VBR between the Kraepelinian and non-Kraepelinian schizophrenic patients (see table 2).

#### DISCUSSION

Very poor prognosis schizophrenic patients were identified with a series of operationalized criteria that were applied cross-sectionally. This group of chronic schizophrenic patients, who for the last 5 years were continuously hospitalized or completely dependent on others for their survival, differed from other chronic

schizophrenic patients on a number of clinical measures, including the frequency with which they were diagnosed schizophrenic by different diagnostic systems, the presence of affective symptoms, the frequency of first-degree relatives who met the criteria for schizophrenia or schizophrenia-related personality disorders, asymmetry of their lateral ventricles, and prospective response to a standard dose of haloperidol. These results are consistent with other studies which have suggested that those patients with the most chronic deteriorated course are substantially unlike other schizophrenic patients (5–14).

It is not surprising that affective symptoms were rare in the chronic Kraepelinian schizophrenic patients. Affective symptoms have previously been shown to be a good prognostic sign. Indeed, the agreement between the present results and previous studies regarding affective symptoms and chronicity lends support to the notion that this population of Kraepelinian schizophrenic patients resembles other, previously studied populations of chronic, poor outcome schizophrenic patients.

The concordance rate for the diagnosis of schizophrenia by various diagnostic systems is a critical area of inquiry, with substantial implications for the conceptualization of schizophrenia. That differing systems yield partially overlapping cohorts of "schizophrenic" patients underlies the necessity for antecedent, concurrent, and prospective validators of the diagnosis of schizophrenia. Because there is no unequivocal consensus as to what constitutes a diagnosis of schizophrenia, it is particularly noteworthy that the Kraepelinian schizophrenic patients met the criteria for schizophrenia in significantly more diagnostic systems than did other chronic schizophrenic patients. Thus, these poor outcome schizophrenic patients seem to possess those core symptoms of schizophrenia that lead virtually all diagnostic systems to classify them as schizophrenic.

Conceptualizations of schizophrenia that have linked chronicity with negative symptoms are partially supported by this cohort of Kraepelinian schizophrenic patients. This group had significantly more severe negative symptoms than the other chronic schizophrenic patients. However, the notion that with increased chronicity there are less severe positive symptoms of schizophrenia is not entirely consistent with the present data. Kraepelinian schizophrenic patients had more severe formal thought disorder as measured by the Thought, Language and Communication Scale. In fact, a similar cohort of patients from our hospital, including some of the patients in this study, demonstrated a weak positive relationship between positive and negative symptoms (26). Thus, these Kraepelinian schizophrenic patients offer the overall impression of more severe symptoms in general, rather than in any particular domain.

It has been repeatedly demonstrated that the morbid risk of schizophrenia and schizophrenia-related personality disorders is significantly higher among firstdegree relatives of schizophrenic patients than among

normal control subjects. In a study that employed the family history method, it was found that the morbid risk of schizophrenia spectrum disorders was higher in a group of chronic schizophrenic patients than in normal control subjects (4). The intriguing new finding that derives from the current work is that Kraepelinian schizophrenic patients had a higher morbid risk of schizophrenia spectrum disorders than other chronic schizophrenic patients. This finding should be viewed with caution given the reported tendency of the family history method to underestimate the prevalence of psychiatric illness (30) and the possible difficulties of reliably diagnosing schizophrenia-related personality disorders by this method. However, given these methodological concerns, one would expect the family history method to diminish apparent group differences rather than increase them. Thus, it can be speculated that among these very poor outcome chronic schizophrenic patients, there is a higher genetic diathesis for schizophrenia than among other, better prognosis patients.

The entire population of schizophrenic patients studied in this cohort had VBRs that were significantly larger than those of age-matched normal control subjects (31). On the basis of previous reports that lateral ventricular enlargement is associated with poor outcome (32, 33), poor response to neuroleptic treatment (9), and negative symptoms (34), the group of severely deteriorated Kraepelinian schizophrenic patients in this study could be expected to have larger VBRs than non-Kraepelinian schizophrenic patients. However, VBR did not differ significantly between the Kraepelinian and other chronic schizophrenic patients. It should be noted that a small difference in VBR between these two chronic populations might not be detected in a sample of this size.

Because of the notion that the schizophrenic process may asymmetrically affect the hemispheres of the brain (35–37), the ratio between left and right lateral ventricles was calculated. The ratio differed significantly between the two schizophrenic populations, confirming results previously reported on a smaller group of this cohort (31). Studies of handedness currently being conducted in our laboratory indicate that the vast majority of schizophrenic patients in our population are right-handed. Hence, these data can be interpreted as consistent with the notion that the poorest outcome schizophrenic patients have a more uneven ventricular enlargement than that which occurs in better prognosis schizophrenic patients.

Retrospective assessment of treatment response is problematic. Unless records are maintained, it is difficult to determine if poor treatment response was a function of poor patient compliance or even inadequate dosing. The prospective trial of haloperidol was a way to confirm that those patients classified as Kraepelinian by prior history were in fact creatment resistant. From this perspective, the study result was without question. The Kraepelinian schizophrenic patients had a significantly poorer response to the stan-

dardized haloperidol treatment than did the better prognosis schizophrenic patients. This result confirms the probable adequacy of prior trials of neuroleptics and supports the validity with which the operationalized criteria for "Kraepelinian" schizophrenia can be used. A somewhat unexpected associated result of the haloperidol study was the very modest response to neuroleptics that was found even among the better prognosis schizophrenic patients; this finding reflects the chronicity of the patient population served by this

typical VA hospital. To establish a new diagnostic entity or meaningful subgroup of schizophrenia will require numerous studies and extensive patient samples. From that perspective, the current data are quite preliminary. Validation of a schizophrenic subgroup, like validation of any diagnostic grouping, would necessitate antecedent, concurrent, and prognostic validators. As a beginning, these results indicate that the powerful antecedent validator of family history is suggestive of a higher premorbid risk of schizophrenia and schizophrenia related disorders in poor outcome Kraepelinian schizophrenic patients. Similarly, descriptive, concurrent validators such as affective symptoms, severity of negative symptoms, and consistency of diagnosis of schizophrenia across various diagnostic systems also distinguish Kraepelinian from other schizophrenic patients. A biological concurrent validator, ventricular asymmetry, is also consistent with the notion that Kraepelinian schizophrenic patients differ from other chronic schizophrenic patients. And finally, the prospective prognostic validator, response to treatment, also differentiates the Kraepelinian subgroup. These potential validators need to be explored in far greater depth, and additional validators need to be tested. The operationalized criteria for defining the Kraepelinian subgroup, or any very poor outcome subgroup, need to be refined. For example, is a 5-year course of severe chronicity more or less useful in defining meaningful and distinct subgroups than a 2- or 3-year course might be? Work is in progress to address these and other issues.

#### REFERENCES

- Research on Mental Illness and Addictive Disorders: Progress and Prospects. A Report of the Board on Mental Health and Behavioral Medicine, Institute of Medicine. Am J Psychiatry 1985; 142 (July suppl)
   Robins E, Guze SB: Establishment of diagnostic validity in
- Robins E, Guze SB: Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126:983–987
- Kraepelin E: Lectures on Clinical Psychiatry. London, Bailliere, Tendall & Cox, 1904
- Kendler KS, Masterson CC, Ungaro R, et al: A family history study of schizophrenia-related personality disorders. Am J Psychiatry 1984; 141:424

  427
- Kendell RE, Brockington IF, Leff JP: Prognostic implications of six alternative definitions of schizophrenia. Arch Gen Psychiatry 1979; 36:25–31
- McGlashan TH: Testing four diagnostic systems for schizophrenia. Arch Gen Psychiatry 1984; 41:141–144
- 7. Stephens JH, Astrup C, Carpenter WT, et al: A comparison of

- nine systems to diagnose schizophrenia. Psychiatry Res 1982; 6: 129–143
- 8. Huber G, Gross G, Schuttler RA: A long-term follow-up study of schizophrenia: psychiatric course of illness and prognosis. Acta Psychiatr Scand 1975; 52:49–57
- Weinberger DR, Bigelow LB, Kleinman JE, et al: Cerebral ventricular enlargement in chronic schizophrenia: an association with poor response to treatment. Arch Gen Psychiatry 1980; 37:11–13
- Crow TJ: Molecular pathology of schizophrenia: more than one disease process? Br Med J 1980; 280:1–9
- Crow TJ: Two dimensions of pathology in schizophrenia: dopaminergic and non-dopaminergic. Psychopharmacol Bull 1982; 18:22-29
- Crow TJ: Two syndromes in schizophrenia? Trends in Neuroscience 1982; 5:351–354
- Kasanin J: The acute schizoaffective psychoses. Am J Psychiatry 1933; 90:97–123
- McGlashan TH: Predictors of shorter-, medium-, and longerterm outcome in schizophrenia. Am J Psychiatry 1986; 143:50– 55
- Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
- 16. Feighner JP, Robins E, Guze SB, et al: Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972; 26:57-63
- Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799-812
- Endicott J, Spitzer RL: A diagnostic review: The Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
- 19. Carpenter WT, Strauss JS, Bartko JJ: Flexible system for the diagnosis of schizophrenia: a report from the International Pilot Study of Schizophrenia. Science 1973; 182:1275–1278
- Schneider K: Clinical Psychopathology. Translated by Hamilton MW. New York, Grune & Stratton, 1959, pp 133–134
- Langfeldt G: Diagnosis and prognosis in schizophrenia. Proc R Soc Med 1960; 53:1047–1052
- 22. Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases. Geneva, World Health Organization, 1979
- Andreasen NC: Thought, language and communication disorders: clinical assessment, definition of terms, and evaluation of their reliability. Arch Gen Psychiatry 1979; 36:1315–1321
- 24. Strauss JS, Carpenter WT: The prediction of outcome in schizophrenia, II: relationships between predictor and outcome variables. Arch Gen Psychiatry 1974; 31:37–42
- Andreasen NC: Negative symptoms in schizophrenia. Arch Gen Psychiatry 1982; 39:784–788
- Rosen WG, Mohs RC, Johns CA, et al: Positive and negative symptoms in schizophrenia. Psychiatry Res 1984; 13:277–284
- 27. Gittelman-Klein R, Klein DF: Premorbid asocial adjustment and prognosis in schizophrenia. J Psychiatry Res 1969; 7:33-35
- Small NE, Mohs RC, Halperin R, et al: A study of the reliability of reported premorbid adjustment in schizophrenic patients. Biol Psychiatry 1984; 19:203–211
- Andreasen NC, Endicott J, Spitzer RL, et al: The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235
- Andreasen NC, Rice J, Endicott J, et al: The family history approach to diagnosis. Arch Gen Psychiatry 1986; 43:421–429
- Losonczy MF, Song IS, Mohs RC, et al: Correlates of lateral ventricular size in chronic schizophrenia, I: behavioral and treatment response measures. Am J Psychiatry 1986; 143:976– 981
- 32. DeLisi LE, Schwartz CC, Targum SD, et al: Ventricular brain enlargement and outcome of acute schizophreniform disorder. Psychiatry Res 1983; 9:169–171
- 33. Williams AO, Reveley MA, Kolakowska T, et al: Schizophrenia with good and poor outcome, II: cerebral ventricular size and its clinical significance. Br J Psychiatry 1985; 146:239–246

34. Andreasen NC, Olsen SA, Dennert JW, et al: Ventricular enlargement in schizophrenia: relationship to positive and negative symptoms. Am J Psychiatry 1982; 139:297-302

35. Buchsbaum MS, Ingvar DH, Kessler R, et al: Cerebral glucography with positron tomography: use in normal subjects and in patients with schizophrenia. Arch Gen Psychiatry 1982; 39:

251-259

 Stevens JR: Schizophrenia and the brain at the 1984 winter workshop, Davos, Switzerland (letter). Arch Gen Psychiatry 1984; 41:816–817

 Kling AS, Kurtz N, Tachiki K, et al: CT scans in subgroups of chronic schizophrenics. J Psychiatry Res 1983; 17:375–384

### Clinical Forms of Severe Tardive Dyskinesia

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The authors describe 19 patients with severe tardive dyskinesia, 11 of whom had a diagnosis of affective or schizoaffective disorder rather than schizophrenia. Most patients had been receiving long-term neuroleptic treatment with few interruptions and had received only one or two different neuroleptics. Frequent eye blinking was the most prevalent prodromal sign of tardive dyskinesia (in seven patients). Four subtypes of tardive dyskinesia could be distinguished: choreoathetosis, tardive dystonia, blepharospasm, and tardive akathisia. Optimal pharmacotherapy most often consisted of combinations of neuroleptics, lithium carbonate, benzodiazepines, and antiparkinsonian drugs. However, after an average of 62 months, only five patients had markedly improved.

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Perhaps the main reason that tardive dyskinesia is emerging as one of the dreaded diseases in psychiatry is the underlying fear that once it develops, it inexorably proceeds to ever more severe forms until total incapacitation results. Severe tardive dyskinesia with major functional impairment undoubtedly occurs, and such cases nearly always pose a difficult

therapeutic challenge. Those concerned about severe tardive dyskinesia find, however, that there is very little literature specifically devoted to this subject; most of the relevant information is buried in the many articles dealing with tardive dyskinesia in general. The special features of severe tardive dyskinesia, such as its clinical characteristics, complications, and problems of management, are worthy of attention in their own right. The present paper attempts to fill the void by addressing clinically relevant issues of severe tardive dyskinesia.

Defining severe tardive dyskinesia adequately is more difficult than it appears at first. The obvious solution of using a global rating of severity from a scale such as the Abnormal Involuntary Movement Scale (AIMS) (1) may give an accurate indication of the level of observable dyskinesia, but it does not reveal whether the dyskinesia has produced any complications. It may not be unreasonable to regard as severe only those cases in which the abnormal movements are accompanied by subjective distress or impaired functioning. Another definition might take a longitudinal view and define severe tardive dyskinesia as that which can no longer be masked by neuroleptics or as a dyskinesia which does not improve after withdrawal of neuroleptics. The latter view might consider severe tardive dyskinesia to be an end stage or an irreversible form of the disorder.

As long as disagreement and uncertainty about the definition of severe tardive dyskinesia exist, the best approach might be to keep in focus all the major dimensions of the problem: severity of abnormal movements, complications, outcome, and management. This paper provides a description of the clinical features, treatment, and outcome of a series of patients with severe dyskinesia who were treated by two of us (G.G. and J.O.C.).

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TABLE 1. Characteristics and Exposure to Neuroleptics of Nine Male and 10 Female Patients With Severe Tardive Dyskinesia

Characteristic	Mean	SD
General		
Age (years)	42.0	16.3
Age at onset of psychiatric illness (years)	29.0	16.5
Number of psychiatric hospitalizations	2.6	2.1
Duration of psychiatric hospitalizations		
(months) <sup>a</sup>	16.9	42.4
Total AIMS score	16.58	4.7
Exposure to neuroleptics before developing		
clear dyskinesia		
Number of months since first exposure to		
neuroleptics	75.0	69.3
Percent of time not taking neuroleptics	12.3	16.6
Number of neuroleptic-free periods	1.6	1.7
Age when neuroleptic was first received		
(years)	30.0	16.6
Total amount of neuroleptics received		
(grams of chlorpromazine equivalents) <sup>b</sup>	967	1309

<sup>&</sup>lt;sup>a</sup>Thirteen patients had been hospitalized for less than 12 months. Five had been hospitalized for 12 months or more. Data from one patient were incomplete.

<sup>b</sup>Eleven patients had received one or two neuroleptics; seven had

<sup>b</sup>Eleven patients had received one or two neuroleptics; seven had received three or more neuroleptics. Data from one patient were incomplete.

#### **METHOD**

The 19 patients chosen for study were those most severely afflicted with tardive dyskinesia among the patients treated by the two of us during the past 10 years. Because of our interest in tardive dyskinesia, we attract a variety of referrals of unusual and difficultto-treat tardive dyskinesia patients from a wide geographic area. Thus, the sample was weighted in favor of the more severe cases and was not typical of an average psychiatric practice. Selection of cases of severe tardive dyskinesia was based chiefly on clinical judgment; we looked for striking abnormal movements as well as subjective distress and some degree of functional impairment. The primary DSM-III diagnoses of the patients were schizophrenia (N=7), schizoaffective disorder (N=3), bipolar disorder (N=3), major depression (N=5), and obsessive-compulsive disorder (N=1). We took over drug management completely or acted as consultants to the referring psychiatrists and made recommendations regarding pharmacotherapy. Management of the original functional psychiatric disorder was an important therapeutic goal in addition to the challenge of treating the severe dyskinesia.

The principal characteristics of the 19 patients with severe tardive dyskinesia are shown in the top part of table 1. The cohort was not particularly old, had nearly equal numbers of men and women, and did not have either chronic or unusually severe psychiatric illness. The number of affective disorder patients was either greater than or close to the number of schizophrenic patients, depending on whether the schizoaffective patients are counted with one or the other category.

The patients' exposure to neuroleptic treatment is summarized in the bottom half of table 1. The small number of neuroleptics used and the relatively short neuroleptic-free periods indicated that continuous neuroleptic treatment with relatively few changes was the general pattern in this group of patients.

We tried to determine the presence or absence of subtle abnormal movements that might have preceded the appearance of more obvious dyskinesia. In seven patients, frequent eye blinking was reported; in two others, twitching of the face and extremities; in one patient, unspecified neck movements; and in another patient, lip smacking. Since these abnormal movements continued while the patients showed increasingly clear evidence of dyskinesia, we assumed that those earliest manifestations were in fact prodromal signs of tardive dyskinesia. In these 11 patients, the prodromal signs were observed at a mean ±SD of 70.1±44.7 months after the first treatment with neuroleptics. It took 8.8±7.3 months for prodromal signs to progress to obvious dyskinesia and 8.7±10.0 months for obvious dyskinesia to become severe.

At the onset of obvious dyskinesia, 12 (63%) of the patients were receiving trifluoperazine or thiothixene. No patient was receiving lithium. Four patients had a gradual onset, and 14 had a sudden onset. When tardive dyskinesia first became obvious, 18 of the 19 patients were taking a steady dose of neuroleptic (mean dose=527 mg/day of chlorpromazine equivalents). At the onset of severe tardive dyskinesia, only eight patients were taking a steady dose, three were taking diminishing doses, and another eight patients had stopped taking neuroleptics as a result of their developing dyskinesia.

With respect to the most prominent and distressing symptoms in each patient, four types of dyskinesia could be distinguished: choreoathetoid dyskinesia (N=7), dystonia (N=8), blepharospasm (N=2), and akathisia (N=2). In addition to the predominant type of abnormal movement, other dyskinesias were usually present, so the subdivision was somewhat arbitrary. For instance, dystonic patients also showed choreiform dyskinesia, and the patients with blepharospasm also showed other signs of tardive dyskinesia. The following case vignettes illustrate the clinical manifestation of the four subtypes.

#### CASE REPORTS

#### Case 1: Choreoathetoid Dyskinesia

Mr. A, a 36-year-old single, white, unemployed musician with a college degree, first had psychiatric symptoms during his last years in high school; they became worse at age 20. He has been treated with antipsychotics at varying moderate doses since that time. At times he shows bizarre ideas, panic, and sexual preoccupations, but he tends to retain interpersonal warmth, charm, a quirky sense of humor, and good interpersonal relationships. When his antipsychotic drug dose is lowered too far, he becomes frightened by his bizarre

fantasies. Whenever his antipsychotic drugs are stopped altogether, he becomes flagrantly manic.

Frequent eye blinking was first noted when Mr. A was 26, after he had been taking antipsychotics for 6 years. Within a year this progressed to very severe dyskinesia with incessant choreoathetoid restless movements of his arms, legs, trunk, and face. Clozapine produced little therapeutic effect other than sedation. On a regimen of haloperidol, 20 mg/day, plus diazepam and diphenhydramine for oculogyric crises, his severe flailing dyskinesia—which interfered even with drinking and eating—rapidly abated; it has stayed much improved for the last 7 years. Mr. A has recently tolerated a reduction of his haloperidol dose to 10 mg/day without increase in movements or psychosis, and he is essentially nonpsychotic, although he has trouble finding a paying job. He is now stable on a regimen of lithium and haloperidol and is engaged to be married.

#### Case 2: Tardive Dystonia

Mr. B, a 27-year-old single electronics technician, had been a shy youth; he developed an acute paranoid psychosis at age 21, with delusions, hallucinations, and a belief that he was Jesus. He improved on a regimen of haloperidol and trihexyphenidyl and returned to work. Two years later, after he had stopped taking haloperidol for 3 weeks, he had a second psychotic episode and became grandiose and expansive. He was then maintained on trifluoperazine. He had had increased eye blinking for about 3 months before obvious dyskinesia developed, 3 years after he had begun antipsychotic treatment. Attempts to manage Mr. B's dyskinesia by shifting to other drugs (haloperidol or perphenazine) and stopping all neuroleptics failed to alter a rapidly worsening dyskinesia with marked dystonia and severe retrocollis, which left him unable to work. When his dose of haloperidol was increased in an attempt to suppress the dyskinesia, he developed gross tremor without improvement in the dyskinesia. On his present regimen of lithium plus diazepam, he is a little less dyskinetic but still has grotesque movements, walks with his neck fully extended, and has dystonic leg, tongue, and facial movements, including blepharospasm. He is able to work but has paranoid ideation, auditory hallucinations, and few social contacts. There has been no further improvement over the past 2 years while he has been taking lithium and diazepam.

#### Case 3: Blepharospasm

Ms. C, a 37-year-old single woman, had a 14-year history of auditory hallucinations, persecutory and grandiose delusions, labile and inappropriate affect, and social withdrawal. She had never been hospitalized; however, full remission of symptoms had not occurred. She revealed exquisite sensitivity to neurological side effects: even small doses of high-potency neuroleptics produced tremor and rigidity, which were only partially relieved by antiparkinsonian drugs. She tolerated thioridazine in low doses only.

Dyskinesia started about 4½ years ago, while she was taking 100 mg/day of thioridazine, with frequent eye blinking and twitching around her mouth. A few months later, blepharospasm commenced and gradually became severe. When she was first evaluated for tardive dyskinesia, Ms. C was showing severe, almost constant, blepharospasm, making it impossible for her to keep her eyes open for more than a few seconds. Other abnormal movements included facial

tics and grimacing, involuntary jaw opening, mild retrocollis and torticollis, and choreiform movements of the lip and tongue. The severe blepharospasm prevented her from driving and reading and caused great social embarrassment, making her reluctant to leave her home.

Treatment efforts during the past 3 years have been largely ineffective. Attempts to substitute another neuroleptic in small doses were unsuccessful. Her dose of thioridazine was reduced to 50 mg/day, however, without signs of psychotic decompensation. The following drugs were tried sequentially for treatment of blepharospasm, with negative results: reserpine, clonazepam, lecithin, propranolol, amantadine, and lithium.

#### Case 4: Tardive Akathisia

Ms. D, a 56-year-old mother of two, first became severely depressed and delusional after her husband and her father-in-law died within a 4-month period. She was hospitalized three times, each time severely depressed, with delusions of guilt and suicidal tendencies.

Antidepressants increased her delusional thinking. Neuroleptics were given intermittently at first, then continuously. When first evaluated for tardive dyskinesia 3 years ago, Ms. D showed marked akathisia: rocking, foot tapping, stamping, continuous torsion movement, and pelvic thrusting. The need to be in constant motion and the subjective distress made this syndrome indistinguishable from acute druginduced akathisia. She also exhibited mild choreiform movements of the lips, tongue, and jaw, which suggested tardive dyskinesia; however, she never complained about the latter symptoms. The unrelenting akathisia led her to avoid social contacts and at times interfered with sleep.

Considerable improvement has occurred during the past 3 years with thioridazine, 50 mg h.s., ethopropazine, 50 mg h.s., and alprazolam, 0.5 mg b.i.d. Her akathisia is mostly quiescent, and her mild orofacial choreiform movements are not distressing. Her psychiatric symptoms have been slowly improving along with the receding akathisia.

#### OUTCOME

Demographic variables, treatment trials, and outcome to date for the 19 patients are summarized in table ?

The tardive dystonia subgroup consisted mostly of men (75%) in contrast to the other groups, which had an excess of women. Patients with dystonia were significantly younger (mean $\pm$ SD age=31.9 $\pm$ 7.2 years) than those with choreoathetosis (54.9 $\pm$ 17.7 years; F=11.2, df=1, 14, p<.005).

From the time the diagnosis of severe dyskinesia was made, the cohort was followed for an average of 62 months (range: 4 months to 15 years). The tardive dystonia subgroup showed the most severe symptoms at baseline as well as at the last rating. The mean AIMS total score for the entire cohort declined from 16.58 at baseline to 12.53 at the last rating (t=2.98, df=18, p<.01), which reflects a 25% improvement. Improvement varied greatly among the 19 patients, and only five improved by at least 50%, which is the usual criterion for clinically significant improvement.

TABLE 2. Characteristics, Treatment, and Outcome of 19 Patients With Severe Tardive Dyskinesia

				AIMS Sc	ore	Current (Best?) Mo	edications	
Type of Dyskinesia and Patient	Sex	Age (years)	DSM-III Diagnosis	During Worst Tardive Dyskinesia	At Last Rating	Drug	Dose (mg/day)	Drugs Tried for Dyskinesia With No Benefit
Choreoathetoid	- OCA	()(213)	Diagnosis	Dyskincsia		Diug	(1116/44)/	With 110 Bellent
dyskinesia								
1	F	73	Major depression	13	11	Phenelzine	45	Imipramine, loxapine
			, .			Diazepam	5	
_	_					Bromocriptine	10	
2	F	73	Major depression	11	11	Thiothixene	4	Haloperidol, amitriptyline,
3	F	73	Major depression	12	19	Diphenhydramine Haloperidol	50 18	thioridazine Reserpine, benzodiazepines,
3	1	73	wajor depression	1.2.	17	Ethopropazine	150	choline, benztropine
						Diphenhydramine	50	Judania, Januara Pana
4	F	51	Schizophrenia,	10	17	Lithium	1800	Deanol, papaverine,
			disorganized			Thiothixene	40	diazepam, haloperidol,
5	M	26	Maior domession	26	15	Carbamazepine		reserpine, lecithin
J	IVI	36	Major depression	26	15	Diazepam Phenytoin	80 300	Lithium, haloperidol, clozapine, deanol, baclofen,
						Doxepin	300	amitriptyline, propranolol,
						Diphenhydramine	400	lecithin
6	M	36	Bipolar disorder	19	5	Haloperidol	10	Deanol, amantadine
_						Lithium		•
7	M	42	Schizophrenia,	13	16	Haloperidol	12	Ethopropazine, diazepam
			undifferentiated			Lithium	900	
						Benztropine Lorazepam	4 1	
Tardive						Lorazepani	1	
dystonia								
8	F	29	Schizophrenia,	20	20	Lithium	_	Clonazepam, diazepam,
			disorganized					baclofen, deanol, thior-
0	17	2.2	n'11'1	24	4.4	0.1	4.400	idazine
9	F	23	Bipolar disorder	21	14	Carbamazepine Lithium	1400 1200	Propranolol, diazepam,
10	M	44	Bipolar disorder	20	16	Lithium	900	reserpine, trifluoperazine Reserpine, L-dopa,
			arpara manaran			Haloperidol	5	baclofen, benztropine,
						Clonazepam	2.5	trihexyphenidyl, diazepam
11	M	29	Schizophrenia,	14	14	Haloperidol	10	Lithium, amantadine,
			paranoid			Biperiden	6	choline, benztropine,
						Desipramine	_	haloperidol, diazepam,
12	M	40	Schizoaffective	22	9	Haloperidol	4	chlordiazepoxide Amantadine, ethopropazine,
	474	,,,	disorder, de-	202		Lithium	600	clonazepam, amoxapine,
			pressed type			Temazepam	45	loxapine
13	M	37	Obsessive-com-	18	17	Haloperidol	10	Propranolol, baclofen,
			pulsive disorder			Benztropine	4	amantadine, choline,
						Clonazepam	1.5	trihexyphenidyl, diphenhy-
14	M	29	Schizoaffective	19	14	Lithium	1200	dramine, L-dopa, deanol
	747	47	disorder, manic	17	17	Molindone	40	Thioridazine, lecithin, lorazepam
			type			AUMINIONIO	10	Totalopani
15	M	27	Schizoaffective	18	11	Lithium	-	Haloperidol, benztropine
nt. t			disorder			Diazepam	40	<u> </u>
Blepharospasm	C	20	Schinon-bassis	n	4	Chlamon	300	A
16	F	38	Schizophrenia, paranoid	9	4	Chlorpromazine Trihexyphenidyl	300 6	Amantadine, benztropine,
17	F	37	Schizophrenia,	20	13	Thioridazine	50	deanol, thiothixene Clonazepam, lecithin,
			paranoid		10	1 moridabilic	30	reserpine, propranolol,
			•					amantadine, haloperidol,
T1:								lithium, thiothixene
Tardive akathisia								
akathisia 18	F	56	Major depression	12	6	Thioridazine	50	Haloperidol, loxapine,
	•	50	Avanjor depression		U	Ethopropazine	50	lecithin, reserpine,
						Alprazolam	1	clonidine, flurazepam,
						•		amantadine, propranolol,
10	r	2.	011 1 1	40	_	ot .	***	L-tryptophan, lorazepam
19	F	26	Schizophrenia,	19	6	Clozapine	500	Haloperidol, molindone,
			undifferentiated					loxapine, lithium, diazepam, lorazepam, propranolol

The data on drug treatment are complex. The current medications, as listed in table 2, were the end result of numerous therapeutic trials and may be assumed to be the optimal drug combinations, at least from among the compounds that were tried. Eighteen of the 19 patients (95%) were taking various combinations of drugs. Fourteen patients (74%) were still taking neuroleptics despite their severe dyskinesia, because attempts to discontinue these drugs had resulted in psychotic decompensation and/or worsening dyskinesia. The neuroleptic dose, however, tended to be modest (mean=398 mg/day of chlorpromazine equivalents). This represents approximately a 25% overall decrease in neuroleptic dose since obvious dyskinesia had developed, but we could find no association between reduction of the dose and improvement in tardive dyskinesia. Antiparkinsonian drugs were helpful in about half of the patients. While these drugs may appear to be an unusual treatment for dyskinesia, we found that 12 of the 19 patients had parkinsonian manifestations (tremor, akathisia, drooling, rigidity) at some time, while also showing dyskinesia. Benzodiazepines were part of the optimal drug regimen in eight of the 19 cases and appeared to be useful adjunctive drugs. Lithium was therapeutic in nine patients, six of them in the dystonia subgroup. A number of theoretically promising compounds (e.g., lecithin, baclofen, propranolol, reserpine, and L-dopa) were not helpful to our patients; they were administered in an unsystematic fashion and were usually combined with other drugs.

#### DISCUSSION

The data we have presented need to be viewed with full awareness of the limitations inherent in the method of our study. The study was conducted in a clinical setting without our being able to control patient selection, assignment to different treatments, and length and frequency of assessments. The strength of the study may in fact arise out of its weakness; namely, by virtue of the clinical rather than laboratory method of data collection, the findings are directly relevant to clinical settings where tardive dyskinesia patients are assessed and treated.

The 19 patients came to us over a 10-year period, most of them by referral from other psychiatrists; some were from out of state. Since we do not know the real "catchment area" from which the cohort was drawn, it is impossible to make informed statements about the prevalence of severe tardive dyskinesia. The only reasonable inference to be drawn is that severe tardive dyskinesia is likely to be quite uncommon; otherwise, we would have seen considerably more cases. The relative rarity of severe tardive dyskinesia has also been suggested in our previous work (2–4).

The demographic characteristics of our group of patients with severe tardive dyskinesia were unremarkable, with no striking features. They contained surprises, however, in comparison to a prior expectations. For instance, the mean age of 42.05 years (at an average of 62 months after severe tardive dyskinesia was diagnosed) is considerably younger than would be expected from the literature, which unequivocally demonstrates that the prevalence and severity of tardive dyskinesia increases with age (5). The age distribution of the cohort (table 2) gives a hint of a possible bimodal distribution, with peaks in the 30s and 70s, although the small size of the sample makes this highly speculative. A preponderance of women with tardive dyskinesia, as suggested by the epidemiological literature (6), was not reflected in our cohort.

Any assumptions that patients with severe tardive dyskinesia tend to come from the ranks of the most severely ill psychiatric patients are contradicted by the data displayed in table 1. These patients with tardive dyskinesia were not chronic and had few, relatively short hospitalizations. The mean age at onset of illness (29 years) was higher than would be expected in severe psychotic illness. The neuroleptic treatment data showed a trend for continuous neuroleptic treatment in amounts that are not unusually high.

The finding that only one or two neuroleptics were used for most patients was unexpected and differs from Mukherjee et al.'s report (7), which found a significant association between number of neuroleptics and moderate tardive dyskinesia, but not between the number and mild tardive dyskinesia. It is possible that patients who later developed tardive dyskinesia had tolerated their neuroleptics better and had had a more reliable clinical response, so that fewer changes had been necessary. Alternatively, the few neuroleptics may be related to the few neuroleptic interruptions, and these two findings may have a common explanation. Since other studies (8, 9) have found an association between prevalence of tardive dyskinesia and drug-free periods, the present research suggests a modification of that hypothesis; drug interruptions and/or drug-free periods may be associated with mild but not severe tardive dyskinesia.

As far as diagnosis is concerned, it might be assumed that since most patients receiving continuous neuroleptic treatment are schizophrenic, most patients with tardive dyskinesia are also schizophrenic. The data indicate that this may not be true for severe tardive dyskinesia. Affective disorder (unipolar and bipolar) patients outnumbered schizophrenic patients in the cohort. The diversity of diagnoses posed a problem in the handling of data. Schizophrenic subjects may differ greatly from nonschizophrenic subjects on a number of important variables, particularly with regard to use of neuroleptics. Separating schizophrenic from nonschizophrenic subjects and analyzing data within these diagnostic subgroups might have revealed different relationships. We did not follow this procedure for two reasons. 1) No meaningful conclusions could be drawn from results obtained from a sample of only seven schizophrenic and 12 nonschizophrenic subjects, especially since there may have been double and possibly higher-order interactions among diagnostic, demographic, and treatment variables. 2) A more controversial issue concerns the validity of diagnostic classification, namely, the categorical versus dimensional nature of mental illness. Schizophrenia may not be a totally separate entity if mental illness is conceived of as dimensional, and schizoaffective psychosis and even bipolar disorder may be conceived of as a continuum. If the four major diagnostic subgroups into which our study patients were divided interrelate in a complex fashion, dichotomizing patients into schizophrenic and nonschizophrenic groups might not be productive or particularly valid. Since this paper focuses on tardive dyskinesia, the diagnostic issues will not be discussed further. The important relationships among diagnosis, severe tardive dyskinesia, and neuroleptics need to be studied in larger samples before conclusions can be drawn. At this point we can only restate that, contrary to expectations, the majority of the patients with severe tardive dyskinesia had a diagnosis other than schizophrenia.

The background variables suggest a profile of the patient with severe tardive dyskinesia which is quite different from that of the typical tardive dyskinesia patient. The modal patient with severe tardive dyskinesia is young, can be of either sex, is not chronically ill or frequently hospitalized, is likely to be nonschizophrenic, and has been treated with only one or two neuroleptics, with few or short interruptions. Severe tardive dyskinesia may therefore be a different disorder from mild tardive dyskinesia, in the sense that different patients develop the two disorders. Our findings point to the need for further research to clarify the characteristics of patients who show vulnerability to severe, as distinct from mild, tardive dyskinesia.

At the onset of obvious tardive dyskinesia, the majority of patients were taking trifluoperazine or thiothixene. Since drug history data clearly documented the extensive use of these neuroleptics, the frequent presence of these two drugs at the time tardive dyskinesia appeared may not reflect a true etiological relationship. Lithium was conspicuously absent at the onset of tardive dyskinesia in patients who subsequently had a severe case. Could lithium have prevented severe tardive dyskinesia in some patients? Laboratory evidence suggests that lithium blocks neuroleptic-induced proliferation of striatal dopamine receptors (10, 11). However, once tardive dyskinesia is manifest, lithium's efficacy in reducing the severity of dyskinetic symptoms is questionable (12). Nevertheless, nine of our 19 patients were receiving lithium at their last evaluation. The coadministration of lithium to these patients probably made it possible to decrease their doses of neuroleptics without psychotic decompensation. An additional advantage of the use of lithium in the phase before tardive dyskinesia became severe might have been amelioration of the affective symptoms.

In the majority of patients, the onset of severe dyskinesia occurred while neuroleptics were being

withdrawn or doses were being reduced in an attempt to deal with the dyskinesia. The effect in our study patients was the opposite of what was intended, namely, the exacerbation of already existing dyskinesia. We assume that dose reduction or neuroleptic withdrawal did not produce the severe tardive dyskinesia but only uncovered it, a phenomenon analogous to that in covert dyskinesia (13–15). The dose reduction or discontinuation may even have served the potentially useful purpose of causing earlier recognition and therefore earlier treatment of the severe tardive dyskinesia.

We made considerable efforts to document the site and time of first occurrence of dyskinesia. Frequent eye blinking, which we observed in seven of the 19 patients, had not been reported as a possible prodromal sign of tardive dyskinesia. Eye-blink rates may reflect central dopaminergic activity (16), and there is a tendency for schizophrenic patients and Parkinson's disease patients treated with L-dopa to show elevated eye-blink rates (17). In view of the generally accepted hypothesis that tardive dyskinesia is associated with overactivity of the nigrostriatal dopamine system, it is possible that increased eye blinking is related to tardive dyskinesia.

Four other patients had varied prodromal signs, which at the time were probably not considered early tardive dyskinesia but in retrospect were almost certainly the first manifestations of it. In fact, one may think of prodromal signs as missed early indications that only become clinically significant after the disorder is clearly evident, whereas early signs of tardive dyskinesia are usually recognized immediately as such. The obvious corollary is to regard eye blinking and unusual jerky movements, even if infrequent and subtle, as possible early signs of tardive dyskinesia in a patient treated with neuroleptics.

#### Clinical Subtypes

Tardive dystonia was the salient movement disorder in eight of the patients with severe tardive dyskinesia. It may be defined as a neuroleptic-induced, late-onset, persistent movement disorder consisting of sustained involuntary twisting movements affecting the limbs, trunk, neck, or face (18). The differentiation between chorea, athetosis, and dystonia in tardive dyskinesia patients is often difficult, because many patients show mixtures of several types of dyskinetic movements at the same time and because intermediate forms exist between tics and grimaces or between choreiform and dystonic limb movements. The much younger age and the predominance of men in our tardive dystonia group, in comparison to patients with other types of tardive dyskinesia, are in agreement with the literature (18, 19).

Current treatment of tardive dystonia is unsatisfactory (18–21). In our series, low to moderate doses of neuroleptics were found to be a necessary evil: without them decompensation was frequently seen. Tetraben-

azine, which is not available in the United States, and high doses of centrally acting antimuscarinic anticholinergic agents, primarily trihexyphenidyl, have been cited in the literature as potential therapeutic agents for dystonia (18, 19, 21); however, any improvement may prove to be temporary (22). Bromocriptine, a dopamine agonist, is the latest compound that shows promise in the treatment of dystonia (23). The particular treatment refractoriness of tardive dystonia and the underlying neuropharmacological differences between it and choreoathetoid dyskinesia are incompletely understood.

Blepharospasm was the major symptom in two patients. More typical choreathetoid features were also present; however, it was blepharospasm that caused distress and impaired functioning. It interfered with driving and reading and led to avoidance of social activities. Patients with the blepharospasm may be afflicted with a subtype of tardive dystonia that is restricted to the eyes. Another hypothesis is that these patients have a neuroleptic-induced version of Meige's or Brueghel's syndrome, a spontaneous extrapyramidal disorder consisting of blepharospasm and oromandibular dystonia (24). The differentiation of Meige's syndrome from tardive dyskinesia is at times exceptionally difficult and may require pharmacological probes (25). From our two cases, little can be said about treatment approaches, but the positive response of one patient to chlorpromazine and trihexyphenidyl and of the other to thioridazine is consistent with the hypothesis that in Meige's syndrome overactivity of both the dopaminergic and the cholinergic systems may be present (26).

We labeled the dyskinetic syndrome in two of our patients tardive akathisia because akathisia dominated the clinical picture. As Stahl (27) pointed out, however, akathisia is a confusing concept, with some features of an extrapyramidal as well as a mental disorder. Similarly, the concept of tardive akathisia is subject to varying definitions, including the notion that it is a variant of tardive dyskinesia and may not be a separate entity. A good deal of controversy also surrounds the question of the presence or absence of subjective distress (27–29), and it appears premature to attempt to distinguish subtypes of akathisia on that basis.

Akathisia in the initial stages of neuroleptic treatment may respond to anticholinergic and antihistaminic drugs (27), benzodiazepines (30), propranolol (31), or clonidine (32), but usually not as readily as druginduced parkinsonian symptoms do. Akathisia that occurs late in neuroleptic therapy, with or without tardive dyskinesia, tends to respond less well to these compounds. It was gratifying to see our two patients with akathisia show marked improvement with 1) clozapine and 2) a combination of low doses of thioridazine, alprazolam, and ethiopropazine. Little can be concluded on the basis of two cases, but we gained the impression that tardive akathisia may be reversible.

#### CONCLUSIONS

The cohort as a whole showed mild improvement after an average of 62 months. This finding can be viewed as encouraging or disappointing, depending on a priori expectations. Five patients improved markedly and no longer showed severe dyskinesia. Thus, 26.3% of our patients with severe tardive dyskinesia were effectively treated, leaving the remaining 14 patients (73.7%) disabled even after our best efforts. However, some of these patients had improved between their baseline rating and their last rating and may continue to do so, which makes the prognosis of even the worst cases of dyskinesia far from hopeless.

The treatment methods we used are best characterized as empirical and clinically oriented. We found that therapeutic approaches based on contemporary neuropharmacological principles (e.g., increasing striatal cholinergic or GABA-ergic influences and/or reducing dopaminergic activity) were often interrupted because of psychotic relapse, ineffectiveness, or parkinsonian manifestations. Innovative treatments such as propranolol, baclofen, and receptor sensitivity modification were mostly unsuccessful with this group, but we were unable to administer these in a carefully controlled way. Somewhat to our surprise, and without intending to practice polypharmacy, we found ourselves treating most patients with an apparently optimum balance of combinations of neuroleptics, lithium, benzodiazepines, and anticholinergic antiparkinson drugs. It would be foolhardy to attempt to provide a rational explanation for the contribution of each drug, and of their interactions, to any overall therapeutic effect. Our ignorance of the mechanism of antidyskinetic effects is hardly surprising in view of the scant knowledge about the pharmacology of tardive dyskinesia, not to mention severe tardive dyskinesia.

The varied diagnoses of our patients may also have contributed to the variety of treatments administered. In particular, the use of lithium in about half of the patients was probably more closely related to its therapeutic efficacy for affective symptoms than for its effect on dyskinesia. Whether schizophrenic patients with severe tardive dyskinesia fare better than similar patients with affective or other nonschizophrenic diagnoses needs to be determined in future studies with larger samples.

#### REFERENCES

- Guy W: ECDEU Assessment Manual for Psychopharmacology. Washington, DC, US Department of Health, Education and Welfare, 1976, pp 534–537
- Gardos G, Samu I, Kallos M, et al: Absence of severe tardive dyskinesia in Hungarian schizophrenic outpatients. Psychopharmacology 1980; 71:29–34
- 3. Gardos G, Cole JO, Perenyi A, et al: Five-year follow-up study of tardive dyskinesia, in Chronic Treatments in Neuropsychiatry. Edited by Kemali D, Racagni G. New York, Raven Press, 1985
- Gardos G, Cole JO: Prognosis of tardive dyskinesia. J Clin Psychiatry 1983; 44:177–179

- Smith JM, Baldessarini RJ: Changes in prevalence, severity, and recovery of tardive dyskinesia with age. Arch Gen Psychiatry 1980; 37:1368–1373
- Kane JM, Smith JM: Tardive dyskinesia prevalence and risk factors: 1959 to 1979. Arch Gen Psychiatry 1982; 39:473

  –481
- 7. Mukherjee S, Rosen, AM, Cardenas C, et al: Tardive dyskinesia in psychiatric outpatients: a study of prevalence and association with demographic, clinical, and drug history variables. Arch Gen Psychiatry 1982; 39:466–469
- 8. Jeste DV, Potkin SG, Sinha S, et al: Tardive dyskinesia: reversible and persistent. Arch Gen Psychiatry 1979; 36:585-590
- 9. Branchey M, Branchey L: Patterns of psychotropic drug use and tardive dyskinesia. J Clin Psychopharmacol 1984; 4:41–45
- Klawans HL, Weiner WJ, Nausieda PA: The effect of lithium on animal models of tardive dyskinesia. Prog Neuropsychopharmacol 1977; 1:53-60
- 11. Pert A, Rosenblatt JE, Siritt C, et al: Long-term treatment with lithium prevents the development of dopamine receptor supersensitivity. Science 1978; 201:171–173
- Cole JO, Gardos G, Rapkin RM, et al: Lithium carbonate in tardive dyskinesia and schizophrenia, in Tardive Dyskinesia and Affective Disorders. Edited by Gardos G, Casey DE. Washington, DC, American Psychiatric Press, 1984
- Gardos G, Cole JO, Rapkin RM, et al: Anticholinergic challenge and neuroleptic withdrawal: changes in dyskinesia and symptom measures. Arch Gen Psychiatry 1984; 41:1030–1035
   Gardos G, Cole JO, Tarsy D: Withdrawal syndromes associated
- Gardos G, Cole JO, Tarsy D: Withdrawal syndromes associated with antipsychotic drugs. Am J Psychiatry 1978; 135:1321– 1324
- 15. Carpenter WT, Rey AG, Stephens JH: Covert dyskinesia in ambulatory schizophrenia (letter). Lancet 1980; 2:212-213
- Karson CN: Spontaneous eye-blink rates and dopaminergic systems. Brain 1983; 106:643-653
- 17. Stevens JR: Eye blink and schizophrenia: psychosis or tardive dyskinesia? Am J Psychiatry 1978; 135:223-226
- Burke RE, Fahn S, Janovic J, et al: Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurol-

- ogy 1982; 32:1335-1346
- Gimenez-Roldan S, Mateo D, Bartolome P: Tardive dystonia and severe tardive dyskinesia. Acta Psychiatr Scand 1985; 71: 488–494
- Burke RE, Fahn S, Janovic J, et al: Tardive dyskinesia and inappropriate use of neuroleptic drugs (letter). Lancet 1982; 1: 1299
- Fahn S: High dosage anticholinergic therapy in dystonia. Neurology 1983; 33:1255–1261
- 22. Wolfe ME, Koller WC: Tardive dystonia: treatment with trihexyphenidyl. J Clin Psychopharmacol 1985; 5:247-248
- Newman RP, LeWitt PA, Shults C, et al: Dystonia: treatment with bromocriptine. Clin Neuropharmacol 1985; 8:328–333
- Marsden DD: Blepharospasm-oromandibular dystonia syndrome (Brueghel's syndrome). J Neurol Neurosurg Psychiatry 1976; 39:1204–1209
- Dilsaver SC, Domino L: Meige's syndrome or tardive dyskinesia? (letter). J Clin Psychopharmacol 1985; 5:362–364
- Stahl SM, Yesavage JA, Berger PA: Pharmacologic characteristics of Meige dystonia: differentiation from tardive dyskinesia. J Clin Psychiatry 1982; 43:445–446
- Stahl SM: Akathisia and tardive dyskinesia. Arch Gen Psychiatry 1985; 42:915–917
- 28. Barnes TRE, Braude WM: Akathisia variants and tardive dyskinesia. Arch Gen Psychiatry 1985; 42:874-878
- Munetz MR, Cornes CL: Distinguishing akathisia and tardive dyskinesia: a review of the literature. J Clin Psychopharmacol 1983; 3:343-350
- Director KL, Muniz CE: Diazepam in the treatment of extrapyramidal symptoms: a case report. J Clin Psychol 1982; 43: 160-161
- Lipinski JF, Zubenko GS, Cohen BM, et al: Propranolol in the treatment of neuroleptic-induced akathisia. Lancet 1983; 1: 685–686
- Zubenko GS, Cohen BM, Lipinski JF Jr, et al: Use of clonidine in treating neuroleptic-induced akathisia. Psychiatry Res 1984; 13:253-259

# The Psychiatrist and Solvent-Inhalant Abuse: Recognition, Assessment, and Treatment

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Solvent-inhalant abuse, existent for a century, has been gradually increasing in several sectors of our society over the last few decades. This form of substance abuse involves a variety of pharmacological agents as well as several target groups at risk. A key strategy for effective intervention is early recognition in clinical as well as other settings. Psychiatrists should appreciate the clinical manifestations of these substances because they often appear in psychiatric settings. Assessment and treatment of the solvent-inhalant abuser must take into account the special pharmacological, demographic, and ecological factors associated with this particular form of substance abuse.

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R eports on volatile-inhalant abuse have focused on clinical description and acute care of emergent complications (1–6). The course of this disorder is a source of confusion. Some authors (2, 7) have viewed it as a disabling, life-threatening problem, but others (8, 9) have emphasized the experimental, benign nature of solvent-inhalant recreational use. "Controlled use" of the "less dangerous" solvent-inhalants has even been recommended (9). Although several million Americans have used this class of drugs for recreational purposes, relatively few texts on substance abuse even mention the category of solvent-inhalant abuse (10).

To remedy this problem, I searched the medical literature by available computer methods; this search was supplemented by my own collection of relevant articles over the last two decades. I scanned my experience with solvent-inhalant abusers over the last 25 years, with special consideration of 99 young patients with a history of solvent-inhalant use, out of a total of 305 young substance abusers whom I had seen over the last 4 years in Minnesota. Participation in a

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World Health Organization working meeting on solvent-inhalant abuse in 1986 provided an opportunity to review and consider current notions about this problem. Tobacco and cocaine, which can be inhalants, are well addressed in the literature and so are not included here.

# NERVOUS SYSTEM AND OTHER MEDICAL COMPLICATIONS

CNS impairment from the solvent-inhalants generally clears in minutes to a few hours. Acute pathological intoxication, delirium, accidents, assault, or sucide attempts can be observed during the intoxication stage. Chronic encephalopathies have been reported from lead-containing gasolines (11), toluene (12), and house paint (13). Rarely, seizures have occurred (14), but these are uncommon and may be due to a variety of causes, including hypoxia, withdrawal, a low pre-existing seizure threshold, or focal neurological damage. Hearing loss and visual impairment have been reported with a variety of compounds, including toluene, paint, printing fluid, and petroleum products (12, 15–17).

Solvents have been observed to produce a clinical picture resembling glomerulonephritis (18, 19) as well as distal renal acidosis (20). Offending agents include cleaning solvents, various other chlorohydrocarbons, paint, and glue. Concurrent alcohol abuse may exacerbate organ damage, especially in the liver. As with alcohol, bone marrow suppression can develop. Local irritation can produce sinusitis, rhinitis, nasal mucosal erosions, epistaxis, laryngitis, and tracheobronchitis (21). These problems usually resolve after some weeks of abstinence.

Sudden death in solvent-inhalant abusers can occur by a variety of mechanisms. Asphyxiation may result from using a bag over the head to inhale the drug or by aspiration of gastric contents (22, 23). Other mechanisms include cardiac arrhythmia, respiratory arrest, and liver failure (24–26).

#### POPULATIONS AT RISK

Adults at risk for solvent-inhalant abuse include those whose work brings them into contact with solvent-inhalants, such as shoemakers (27), sandal makers (28), cabinetmakers (29), and printers (30). To this list, I would add hair stylists; janitors and maintenance workers; painters; people working in gas stations and car, motorcycle, or bicycle repair shops; workers in dry cleaning establishments; and those involved in the refinement of petroleum products or the manufacture of products containing solvent-inhalant substances. Increased availability of other solvent-inhalants in the workplace has led to increased reporting of solvent abuse cases over the last half-century (31, 32). Medical workers for more than 100 years have been at risk for abuse of ether (33–35), chloroform (36, 37), trichloroethylene (38, 39), and, more recently, halothane, at times with fatal results (40).

Children and adolescents are at risk in any community (8) but are most at risk in communities with widespread unemployment, poverty, marital and family disruption, substance abuse among adults, community disorganization, minority status, negative selfimage, limited recreational outlets, and/or absence of adult supervision for sports and hobbies (7, 41–45). Young students away from home in boarding schools may be at risk for epidemic use (46). Young users are usually 7 to 19 years old, but use has been reported in children as young as 4 to 6 years (47, 48). Youthful abusers obtain solvent-inhalants from the home, school, grocery stores, hobby stores, hardware stores, gas stations, paint stores, institutional cleaning supply stores, and gas tanks (cars, motorcycles, tractors, chain saws, unattended machinery). They have abused gasoline, glue, naphtha, paint, lighter fluid, nail polish remover, clothing spot remover, marker pens, deodorants, kerosene, aerosol cans (e.g., food, spray paint, hair spray), typing correction fluid, gas jets in school science laboratories, nitrous oxide (used to enhance acceleration in racing vehicles), lacquer thinner, transmission fluid (toluene), gun cleaning solvents (in Army recruits), and fire extinguishing agents (49-53). Reports of childhood sniffing go back more than 25 years (54). Since that time solvent-inhalant abuse has shifted to larger numbers of older adolescents and even adults

The psychiatrist should consider the possibility of solvent-inhalant abuse in special patient populations. Crites and Schuckit (57) recommended routine inquiry regarding solvent-inhalant abuse with "all adolescents in trouble." Mentally retarded adolescents and young adults at risk include not only those whose mental retardation predated the substance abuse (6, 58) but also those in whom solvent-inhalant abuse produced the mental retardation (59). Uremic patients undergoing hemodialysis have become addicted to the denatured ethyl alcohol used to clean the skin and dialysis equipment (60). Over-the-counter nasal inhalants containing stimulant vasoconstrictors have also been abused (61–63). Some homosexuals have sniffed amyl and butyl nitrite to relax inhibitions, delay ejaculation, and relax the anal sphincter during penile penetration. Typical users sniff nitrites a few to dozens of times on

any one occasion (64). Substance abusers from lower socioeconomic backgrounds have abused industrial solvents when unable to purchase more expensive drugs (65, 66). Substance abusers incarcerated in jails, workhouses, and prisons—deprived of their drugs of choice—abuse solvent-inhalants (67–69). This can also occur in other isolated settings, such as Army barracks and Navy ships.

Solvents can be also taken by ingestion. Spray disinfectant, hair spray, and chloroform have been diluted and ingested along with beer or mixer (70, 71).

#### CLINICAL ASSESSMENT

Family assessment is critical in the case of child, adolescent, and mentally retarded solvent-inhalant abusers. Common factors in these families include many young children in the family, a single parent, parental substance abuse (including solvent-inhalant abuse), and parental mental retardation, mental disorder, or personality disorder (68, 72, 73). Child abuse or neglect should be considered and ruled out.

Patients often take a variety of solvent-inhalants or misidentify them (50); therefore, collateral information should be sought to confirm the history as obtained from the patient. Laboratory analysis of the substance may be needed.

Patients should be assessed for damage to the CNS, peripheral nervous system, kidneys, liver, lungs, heart, and bone marrow (74). Nutritional deficiency, infections of the respiratory tract and urogenital systems, and trauma may result from inadequate self-care and poor judgment (10). Children and adolescents may manifest declining school performance, less interest in and skill at sports, or incorrigibility (41). Employees often produce less, alienate their co-workers, and injure themselves. Homosexuals may be less discerning or more promiscuous in seeking sexual partners while using inhalants, thus exposing themselves to the risk of violence, venereal disease, or acquired immune deficiency syndrome (AIDS). Pregnant women can induce a fetal solvent-inhalant syndrome in their offspring (75)

Physical examination may provide evidence of recent use. Glue, white flecks of typing correction fluid, or other substances may be noted about the nose or mouth, on the hands, or on the clothes. Inflammation or erosions of nasal membranes or discharge from the paranasal sinuses may be observed. Depending on the type of solvent-inhalant drug and the duration of use, there may be peripheral nervous system findings or signs of intoxication, withdrawal, or CNS damage.

Specific biological tests for most solvent-inhalants are not widely available, a fact that may lead to an increase in use of these agents in this era of urine monitoring outside of medical auspices. An exception is tetraethyl lead gasoline: the lead can be demonstrated in the chronic abuser by basophilic stippling of the red blood cells, increased lead levels on 24-hour

urine testing, or increased erythrocyte protoporphyrin level (76). Psychometric testing of solvent-inhalant abusers can be useful in demonstrating impaired memory and attention span, poor concentration, cerebellar dysfunction, or impairment of nonverbal intelligence (77).

#### **TREATMENT**

In one study of 105 young gasoline abusers (78), 12 of the subjects were seen clinically on four or more occasions with repeated gasoline sniffing. Another follow-up study of adolescent glue sniffers (79) found that a substantial minority abused other drugs, committed criminal acts, and were unemployed. Solvent-inhalant substances are well-known as stepping stones to subsequent abuse of other drugs (7, 48, 66, 80–82). These data suggest that adequate treatment, with long-term care and monitoring, should be provided.

Most hepatic, renal, hematopoietic, pulmonary, and even CNS damage from solvent-inhalants is repaired with abstinence and time alone. Incomplete recovery or even permanent disability can result if detection and treatment are delayed (83). If lead poisoning is present, chelating agents (penicillamine, dimercaprol [British anti-lewisite]), should be administered to hasten excretion.

Withdrawal symptoms associated with chronic, heavy use of solvent-inhalants consist of tremulousness, tachycardia, disorientation, hallucinations, delusions, seizures, and agitation. These symptoms begin within hours or a few days after cessation of use. Patients usually respond to a long-acting sedative drug (such as phenobarbital or diazepam), given in doses sufficient to produce a calm, seizure-free state. The medication is then withdrawn over a 5–10-day period.

Chronic seizures may develop in patients who have abused neurotoxic agents over months or years. Medications with low abuse potential, such as diphenylhydantoin, should be prescribed. If the patient remains stable and the EEG returns to normal, it may be possible to withdraw the antiseizure medication after several months to see whether the seizures resume.

Helping the patient establish and maintain abstinence is accomplished by reducing access to the solvent-inhalant. In 1985 (76), it was reported that several children who were unable to maintain abstinence in their own disorganized family setting stopped the practice when placed in supervised foster homes. Milieu changes can include changing school, friends or playmates, community of residence, or occupation, as in the case of Mr. A.

Case 1. Mr. A, a 28-year-old hair stylist, came for medical treatment for shortness of breath. His breath sounds were reduced, his exercise tolerance was poor, and his chest X-ray showed bilateral diffuse granulomatous pulmonary change. He stated that he had been inhaling hair spray at work over the previous several years. During a 6-week treatment period

and leave of absence from work, he was able to cease all inhalant use. His pulmonary status showed mild improvement. On return to work, however, he could not restrain himself from again inhaling hair spray. A job change was recommended, and he obtained training as a barber. In this occupation, he was able to avoid hair spray use and recovered from his substance abuse.

Once abstinence is achieved, the clinician must be concerned with helping the patient cope with and adjust to life while abstinent. Unless changes are undertaken in the patient's family or social milieu, recurrence is likely. The following case provides an example.

Case 2. Bryan, a 16-year-old student, came for creatment complaining of fatigue, trouble with concentration and memory, decline in grades, and inability to maintain his former skill at sports. Since his liver was enlarged and results of urinalysis were abnormal, serological tests for hepatic and renal function were obtained. The results of these tests were markedly abnormal. Although he had denied substance abuse, when presented with these data Bryan admitted to increasing sniffing of gasoline, kerosene, and clearing solvents over the previous 2 years. The family agreed to clinical monitoring of his laboratory findings and they were willing to ensure his abstinence from solvents, but the refused family counseling for themselves or admission to a drug treatment program for the patient. The patient discontinued his solvent abuse but came for treatment 3 years later at age 19 for cannabis and alcohol abuse.

Various psychotherapies, sociodrama, vocational rehabilitation, and other approaches can be used to treat solvent-inhalant abuse, depending on local resources (84). It may be necessary to treat ensuing panic, mania, paranoia, organic brain syndrome, sexual dysfunction, major depression, and other psychiatric conditions (85). A holistic approach to the patient facilitates full recovery, as in the case of Ms. C.

Case 3. Ms. C, a 44-year-old woman employed in a cleaning establishment, complained of increasing fatigue, somnolence, tremor, and lack of coordination. Her liver was enlarged and tender, and results of hepatic serological tests were markedly abnormal. She readily admitted to carbon tetrachloride inhalation at work over the previous few years, with a marked increase in the frequency of sniffing over the last several weeks. Following the early phase of abstinence she manifested symptoms of a major depression, which increased in severity over a 4-week period despite improvements in her hepatic function. Antidepressant medication and weekly psychotherapeutic sessions were initiated. Subsequently, she made an uneventful recovery and was able to return to work at the cleaning establishment, in a position that did not involve exposure to solvents.

Enhancing personal and ethnic self-identity has been suggested as an intervention strategy in minority communities (86–88). If a particular solvent-inhalant is being abused during an epidemic, it may be possible to add a noxious agent to the substance, such as mustard oil, horseradish essence, or another benign nauseant (42, 53, 89). In one state the law mandates the addi-

tion of sulfur dioxide to industrial nitrous oxide (90). Legislation regarding aerosol propellants should be considered if the public's health warrants it (91). Creative social approaches during epidemics among children and adolescents have included instituting recreational and sports programs, hiring counselors, reducing the adult-to-child ratio in institutional settings, involving community police officers, and obtaining volunteers from nearby professional schools (45, 92–94).

Innovative approaches are also necessary in managing nitrite inhalant abuse by homosexual patients. One educational approach consists of providing instruction on alternate means for achieving the same objective, such as squeezing the erected glans penis in order to delay premature ejaculation or self-relaxation methods to relieve social phobia, as in the case of Mr. D.

Case 4. Mr. D, a 22-year-old waiter who had tested positive for human T-lymphocyte virus (HTLV), was referred for treatment due to inability to cease amyl and butyl nitrite abuse (up to 100 "hits" between Friday and Sunday). He had tried to do so but experienced premature ejaculation during sexual activity while abstinent. When he resumed nitrite abuse, he also resumed promiscuous sexual activitya practice he was trying to stop. A homosexual self-help group was valuable in supporting his recovery. He did not develop AIDS, and he responded to treatment for his nitrite abuse, premature ejaculation, and compulsive sexual promiscuity. A key step in his treatment consisted of abstinence from all drugs and alcohol, since any substance use resulted in return to nitrite abuse. At first he was unwilling to give up use of alcohol and cannabis. In time he appreciated that he had to maintain abstinence from all recreational drugs.

#### **REFERENCES**

- 1. Barnes GE, Vulcano BA: Bibliography of the solvent abuse literature. Int J Addict 1979; 14:403-421
- Taher SM, Anderson RJ, McCartney R, et al: Renal tubular acidosis associated with toluene "sniffing." N Engl J Med 1974; 290:765–768
- Valpey R, Sumi SM, Copass MK, et al: Acute and chronic progressive encephalopathy due to gasoline sniffing. Neurology 1978; 25:507–510
- Hansen KS, Sharp FR: Gasoline sniffing, lead poisoning, and myoclonus. JAMA 1978; 240:1375–1376
- Fischman CM, Oster JR: Toxic effects of toluene: a new cause of high anion gap metabolic acidosis. JAMA 1979; 241:1713–1715
- 6. Goldings AS, Stewart HM: Organic lead encephalopathy: behavioral change and movement disorder following gasoline inhalation. J Clin Psychiatry 1982; 43(2):70–72
  7. Epstein MH, Wieland WF: Prevalence survey of inhalant abuse.
- 7. Epstein MH, Wieland WF: Prevalence survey of inhalant abuse.

  Int J Addict 1978; 13:271–284
- Watson JM: Solvent abuse and adolescents. Practitioner 1984; 228:487–490
- 9. Bowers AJ, Sage LR: Solvent abuse in adolescents: the who? what? and why? Child Care Health Dev 1983; 9:169-178
- Westermeyer J. A Clinical Guide to Alcohol and Drug Problems. Philadelphia, Praeger, 1986
- 11. Prockop LD, Karampelas D: Encephalopathy secondary to abusive gasoline inhalation. J Fla Med Assoc 1981; 68:823–824
- Lazar RB, Ho SU, Melen O, et al: Multifocal central nervous system damage caused by toluene abuse. Neurology 1983; 33:1337-1340
- 13. Bruhn P, Arlien-Soborg P, Gyldensted C, et al: Prognosis in

- chronic toxic encephalopathy: a two-year follow-up study in 26 house painters with occupational encephalopathy. Acta Neurol Scand 1981; 64:259–272
- Allister C, Lush M, Oliver JS, et al: Status epilepticus caused by solvent abuse. Br Med J 1981; 283:1156
- Ehyai A, Freemon FR: Progressive optic neuropathy and sensorineural hearing loss due to chronic glue sniffing. J Neurol Neurosurg Psychiatry 1983; 46:349–351
- Metrick SA, Brenner RP: Abnormal brainstem auditory evoked potential in chronic paint sniffers. Ann Neurol 1982; 12:553-556
- Bergholtz LM, Odkvist LM: Audiological findings in solvent exposed workers. Acta Otolaryngol (Suppl) 1984; 412:109– 110
- Ravnskov U: Acute glomerulonephritis and exposure to organic solvents in father and daughter. Acta Med Scand 1979; 205: 581-582
- Ravnskov U, Forsberg B, Skerffving S: Glomerulonephritis and exposure to organic solvents: a case-control study. Acta Med Scand 1979; 205:575–579
- Streicher HZ, Gabow PA, Moss AH, et al: Syndromes of toluene sniffing in adults. Ann Intern Med 1981; 94:758–762
- 21. Covalla JR, Strimlan CV, Lech JG: Severe tracheobronchitis from inhalation of an isobutyl nitrite preparation. Drug Intell Clin Pharm 1981; 15:51-52
- Anderson HR, Dick B, Macnair RS, et al: An investigation of 140 deaths associated with volatile substance abuse in the United Kingdom (1971–1981). Hum Toxicol 1982; 1:207–221
- Anderson HR, Macnair RS, Ramsey JD: Deaths from abuse of volatile substances: a national epidemiological study. Br Med J 1985; 290:304–307
- Andriukin AA: Toxic effect of dichloroethane on the cardiovascular system. Klin Med (Mosk) 1979; 57:43–47
- Cronk SL, Barkley DE, Farrell MF: Respiratory arrest after solvent abuse. Br Med J 1985: 290:897–898
- Garriot J, Petty CS: Death from inhalant abuse: toxicological and pathological evaluation of 34 cases. Clin Toxicol 1982; 1:257-263
- Arbbriti G, Sirfacusa A, Cianchetti C, et al: Shoe-makers' polyneuropathy in Italy: the aetiological problem. Br J Ind Med 1976; 33:92–99
- 28. Yamamura Y: n-Hexane neuropathy. Folia Psychiatr Neurol Jpn 1969; 23:15-47
- Herskowitz A, Ishii N, Schaumburg H: n-Hexane neuropathy: a syndrome occurring as a result of industrial exposure. N Engl J Med 1971; 285:82-85
- 30. Paulson GW, Waylonis GW: Polyneuropathy due to *n*-hexane. Arch Intern Med 1976; 136:880–882
- 31. Knabenhans PJ: Über psychische Symptome bie vergiftungen mit modernen gewerblichen Lösungsmitteln (On psychic symptoms from poisoning with modern industrial solvents). Schweiz Arch Neurol Psychiatr 1941; 48:232–271
- 32. Knabenhans PJ: Über psychische Symptome bie vergiftungen mit modernen gewerblichen Lösungsmitteln (On psychic symptoms from poisoning with modern industrial solvents). Schweiz Arch Neurol Psychiatr 1942; 49:128–164
- Beluze: De l'etheromanie (On ether addiction). Annales d'Hygiène Publique et de Medicine Legale 1886–1887; 15:539–557
- 34. Joel E: Aethersucht (Ether addiction). Dtsch Med Wochenschr 1928; 54:1081–1083
- 35. Kerr N: Ether inebriety. JAMA 1891; 17:791-794
- Kornfield S, Bikeles G: Ein Fall von Chloroformilsmus (A case of chloroform addiction). Wien Klin Wochenschr 1893; 6:64
- 37. Nevole S: Pripad chloroformove toxikomanie (A case of chloroform addiction). Cas Lek Cesk 1941; 80(17):602-607
- 38. Jordi A: Missbrauch von Trichloraethylen durch Jugencliche zur Hypnose—Tri-sucht bei einem Sekundarchuler: Beitrag zur Kenntnis der Giftwirkung (Abuse of trichloroethylene by adolescents for hypnosis—tri-addiction in a secondary school pupil: contribution to the information on the toxic effect). Schweiz Med Wochenschr 1937; 67(52):1238–1240
- 39. Van Vliet AGM: Een geval van toxische psychose bij

- trichloorethyleenzucht (A case of psychosis in trichloroethylene addiction). Ned Tijdschr Geneeskd 1959; 103(2):75-78
- 40. Spencer JD, Raasch FO, Trefny FA: Halothane abuse in hospital personnel. JAMA 1976; 235:1034-1035
- 41. Kaufman A: Gasoline sniffing among children in a Pueblo Indian village. Pediatrics 1973; 51:1060-1064
- 42. Cohen S: Inhalant abuse. Drug abuse & Alcoholism Newsletter 4(9), 1975
- 43. Padilla ER, Padilla AM, Morales A, et al: Inhalant, marijuana, and alcohol abuse among barrio children and adolescents. Int J Addict 1979; 14:945-964
- 44. Gilbert J: Deliberate metallic paint inhalation and cultural marginality: paint sniffing among acculturating central California youth. Addict Behav 1983; 8:79-82
- 45. Beauvais F, Oetting ER, Edwards RW: Trends in the use of inhalants among American Indian adolescents. White Cloud Journal 1985; 3(4):3-11
- 46. Schottstaedt MF, Bjork JW: Inhalant abuse in an Indian boarding school. Am J Psychiatry 1977; 134:1290-1293
- 47. Berkowitz FE, Booth WRC: Glue-sniffing in a young child. So Afr Med J 1978; 54:622
- 48. Reed BJF, May PA: Inhalant abuse and juvenile delinquency: a control study in Albuquerque, New Mexico. Int J Addict 1984;
- 49. Cohen S: Glue sniffing. JAMA 1975; 231:653-654
- 50. Tenenbein M, deGroot W, Rajani KR: Peripheral neuropathy following intentional inhalation of naphtha fumes. Can Med Assoc J 1984; 131:1077-1079
- 51. Steadman C, Dorrington LC, Kay P, et al: Abuse of a fireextinguishing agent and sudden death in adolescents. Med J Aust 1984; 111:115-117
- 52. Ackerly WC, Gibson G: Lighter fluid "sniffing." Am J Psychiatry 1964; 120:1056-1061
- 53. King GS, Smialek JE, Troutman WG: Sudden death in adolescents resulting from the inhalation of typewriter correction fluid. JAMA 1985; 253:1604-1606
- 54. Lawton JJ, Malmquist CP: Gasoline addiction in children. Psychiatr Q 1961; 35:555-561
- 55. Hershey CO, Miller S: Solvent abuse: a shift to adults. Int J Addict 1982; 17:1085-1089
- 56. Keeler MH, Reifler BC: The occurrence of glue sniffing on a university campus. J Am Coll Health Assoc 1967; 16:69-70
- 57. Crites J, Schuckit MA: Solvent misuse in adolescents at a community alcohol center. J Clin Psychiatry 1979; 40:39-43
- 58. Carroll HG, Abel GG: Chronic gasoline inhalation. South Med J 1973; 66:1429–1430
- 59. Lewis JD, Moritz D, Mellis LP: Long-term toluene abuse. Am J Psychiatry 1981; 138:368-370
- 60. DeSanto NG, Perna N, DiPaola E, et al: Ethyl alcohol sniffing by patients undergoing hemodialysis. JAMA 1975; 234:841-842
- 61. Pentel P: Toxicity of over-the-counter stimulants. JAMA 1984; 252:1898-1903
- 62. Escobar JI, Karno M: Chronic hallucinosis from nasal drops. JAMA 1982; 217:1859–1860
- 63. Schoelzel EP, Menzel ML: Nasal sprays and perforation of the nasal septum. JAMA 1985; 253:2046
- 64. Israelstam S, Lambert S, Oki G: Poppers, a new recreational
- drug craze. Can Psychiatr Assoc J 1978; 23:493-495
  65. Prockop LD, Alt M, Tison J: "Huffer's" neuropathy. JAMA 1974; 229:1083-1084
- 66. Szapocznik J, Daruna P, Scopetta MA, et al: The characteristics of Cuban immigrant inhalant abusers. Am J Drug Alcohol Abuse 1977; 4:377-389
- 67. Press E, Done AK: Solvent sniffing: physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents, I. Pediatrics 1967;

- 39:451-461
- 68. Press E, Done AK: Solvent sniffing: physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents, II. Pediatrics 1967;
- 69. Samples VL: 'Sniffing' at McNeil Island. Am J Correction 1963; 30(3):11, 13, 27
  70. Morse JMD, Thomas E: Hepatic toxicity from disinfectant
- abuse. JAMA 1984; 252:1904
- 71. Storms WW: Chloroform parties. JAMA 1973; 225:160
- 72. Blatherwick CE: Understanding glue sniffing. Can J Public Health 1972; 63:272-276
- 73. Kupperstein LR, Susman RM: A bibliography on the inhalation of glue fumes and other toxic vapors: a substance abuse practice among adolescents. Int J Addict 1968; 3:177-197
- 74. Schikler KN, Lane EE, Seitz K, et al: Solvent abuse associated with pulmonary abnormalities. Adv Alcohol Subst Abuse 1984; 3:75-81
- 75. Goodwin JM, Geil C, Grodner B, et al: Inhalant abuse, pregnancy, and neglected children (letter). Am J Psychiatry 1981; 138:1126
- 76. Gasoline sniffing and lead toxicity among siblings—Virginia. Mortality and Morbidity Weekly Report 1985; 34(29):449-455
- 77. Allison WM, Jerome DWA: Glue sniffing: a pilot study of the cognitive effects of long-term use. Int J Addict 1984; 19: 453-458
- 78. Remington G, Hoffman BF: Gas sniffing as a form of substance abuse. Can J Psychiatry 1984; 29:31-35
- 79. Suwaki H: A follow-up study of adolescent glue-sniffers in Japan. Br J Addict 1983; 78:409-413
- 80. Clements JE, Simpson R: Environmental and behavioral aspects of glue sniffing in a population of emotionally disturbed ado-
- lescents. Int J Addict 1978; 13:129–134
  81. D'Amanda C, Plumb MM, Taintor Z: Heroin addicts with a history of glue sniffing: a deviant group within a deviant group. Int J Addict 1977; 12:255-270
- 82. Watson JM: Solvent abuse: a retrospective study. Community Med 1979; 1:153-156
- Tsushima W, Towne W: Effects of paint sniffing on neuropsychological test performance. J Abnorm Psychol 1977; 86:
- 84. Stybel LJ: Psychotherapeutic options in the treatment of child and adolescent hydrocarbon inhalers. Am J Psychother 1977; 31:525-532
- 85. Massengale ON, Glaser HH, LeLievre RE, et al: Physical and psychological factors in glue sniffing. New Engl J Med 1963; 269:1340-1343
- 86. Barnes G: Solvent abuse: a review. Int J Addict 1979; 14:27-43
- 87. Goldstein G: Inhalant abuse among the Pueblo tribes of New Mexico, in Third Technical Review on Inhalant Abuse. Rockville, Md, National Institute on Drug Abuse, 1976
- 88. Nurcombe B, Bianchi G, Money J, et al: A hunger for stimuli: the psychosocial background of petrol inhalation. Br J Med Psychol 1970; 43:367-382
- 89. Rubin T, Babbs J: The glue sniffer. Federal Probation 1970; 34:23-28
- 90. Schwartz RH, Calihan M: Nitrous oxide: a potentially lethal euphoriant inhalant. Am Fam Physician 1984; 30(5):171-172
- 91. Nicholl AM: The inhalants: an overview. Psychosomatics 1983; 21:914-921
- 92. Merrill E: Problems of children stuck on glue. Community Care 1978; 221:116-118
- 93. Masterton G: The management of solvent abuse. J Adolesc 1979; 26:65-75
- 94. Sourindhrin I, Baird JA: Management of solvent misuse: a Glasgow community approach. Br J Addict 1984; 79:227-232

### Assault Experiences of 100 Psychiatric Inpatients: Evidence of the Need for Routine Inquiry

Andrea Jacobson, M.D., Ph.D., and Bonnie Richardson, M.D.

The authors obtained complete histories of all experiences of being physically or sexually assaulted from 100 psychiatric inpatients, using a structured interview with well-defined assault scales and a detailed inquiry into circumstances surrounding the assault. The majority (81%) of patients had experienced major physical and/or sexual assault. The circumstances associated with the assaults, the patients' perceptions of the effects of the assaults, and previous therapists' lack of awareness of the assaults are discussed. On the basis of these findings the authors recommend routine inquiry into patients' assault history.

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P sychiatrists rarely ask patients whether they have been physically or sexually assaulted, despite the last decades of research on child abuse, spouse abuse, sexual molestation, incest, and rape (1–3). One of us (A.J.), wondering how much of this history was being missed, began to ask patients routinely whether they had ever been assaulted. The amount of history that emerged on questioning suggested that the prevalence of assault experiences might be high enough to justify routine inquiry. This study was designed to determine in a more rigorous way the prevalence of experiences of physical and sexual assault in an inpatient population and to consider the value of routine inquiry.

Previous studies have varied in their findings of prevalence of assault history reported among psychiatric patients. For example, regarding sexual assault of children, Lukianowicz (4) suggested a prevalence of 4% for incest among psychiatric patients but noted that many cases may have been missed. Rosenfeld (5) reported a prevalence of 33% for incest among adolescent patients but had a sample of only 18 patients. Husain and Chapel (6) reported that 14% of a large sample of adolescent inpatient girls reported verifiable incest in response to specific questioning, but they did not include data on sexual assault outside the family or assault not involving intercourse within the family.

Carmen et al. (7) reported a chart review of 188 adolescent and adult inpatients in 1984. Retabulation of their data produces a prevalence of 20% for childhood and/or adult sexual assault and a prevalence of 35% for childhood and/or adult physical assault. Overall, 43% of their sample had experienced physical and/or sexual abuse, and another 7% were suspected to have been abused. However, this study did not distinguish childhood from adult experiences, although it is reasonable to expect that childhood and adult assault experiences may have different developmental effects as well as different effects on therapeutic relationships.

There are methodological difficulties with the current literature on the prevalence of assault experiences. Standardized scales have not been used in many studies. Chart reviews have been the primary method of gathering data, but assault history in particular is probably underestimated by this method because patients may be reluctant to volunteer such information. In some studies the population sampled was so specific that the results cannot be generalized to the adult psychiatric population. Adolescent and preadolescent girls, for example, are at maximum risk for incest (5). Calculating a prevalence rate of sexual assault over the entire period of childhood based on adolescent prevalence rates would generate an inflated prevalence rate for childhood sexual assault.

In addition to the lack of information on the prevalence of specific types of assault, such as sexual assault during childhood, there is also a lack of information on the co-occurrence of two types of assault history, such as physical assault during childhood and sexual assault during adult life. The study of Carmen et al. (7), the broadest study of assault experiences among psychiatric patients, reported that 12% of their sample had experienced both physical and sexual assault (data retabulated), but the relationship be-

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tween childhood and adult assault cannot be determined from their data.

Some studies focused primarily on type and amount of assault and provided no information on such variables as secrecy surrounding the assault, involvement of other family members, alcohol or drug use, and the patient's perception of the effects of the assault.

In the study presented here, patients were interviewed directly and at length about assault experiences. We wanted to be able to describe not only the events of the assaults and the identity of the assailants but also other characteristics of the assault relationship that appeared relevant to psychiatric treatment, and we wanted data about the occurrence of different kinds of assault in the same patient.

#### **METHOD**

All subjects were psychiatric inpatients at a large, university-affiliated county hospital, and all were admitted during a 2-month period. The sample consisted of the first 100 patients over 18 years old (50 men, 50 women) who were stabilized, agreed to participate after the nature of the study had been explained, and completed adequate interviews. Two hundred thirtyseven patients were eligible for the interviews. Seventy patients were not approached for the interview because of very brief admissions, transfer before stabilization, absconding from the hospital, discharge against medical advice, or administrative error. Fiftyfour patients refused to participate. Thirteen of the patients who participated gave invalid interviews. Overall, 100 valid interviews were obtained from among 237 eligible patients.

The chart diagnoses of the patients interviewed included affective disorders (32%), schizophrenia and other psychoses (29%), personality disorder and substance abuse (17%), and other diagnoses, including adjustment disorders, neuroses, and anorexia (22%). These diagnoses were representative of all patients admitted to the psychiatric services, except for an undersampling of patients with schizophrenic diagnoses (29% in the sample interviewed versus 42% in the total sample admitted).

The majority of the patients interviewed were white (81%), and most of the rest were black (18%). The median age was 29 (range=18-75 years). Half of the patients in the sample had never married; the remainder were about evenly divided between currently married and previously married. The median educational attainment was high school graduation, but since 40% of the sample had never worked or were unskilled, the social status (Hollingshead and Redlich) of the patients clustered in classes IV and V (64% of the sample).

A highly detailed semistructured interview, the Physical and Sexual Assault Experiences Interview, was developed for this study. A wide variety of kinds of physical and sexual assault were categorized into four types of assault. 1) Physical assault as a child included

child abuse and physical abuse by peers. 2) Physical assault as an adult included abuse by a spouse and assault and battery. 3) Sexual assault as a child included incest, child molestation, and sexual abuse by peers. 4) Sexual assault as an adult included marital rape, rape, and sexual assault other than rape. Questions about verbal assault were not included in the interview.

Levels of severity of assault were defined by assault scales. The 10-item physical assault scale was modified slightly from Straus's Conflict Tactics Scales (8). The 15-item sexual assault scale was based on several previous scales (9, 10). Both the physical and the sexual assault scales contained major assault subscales, consisting of the most severe levels of assault. Major physical assault ranged from "kicked, bit or hit with fist," through "burned you" and "beat you up," to "used a knife or gun on you." Major sexual assault included all acts involving physical contact with the genitals of the victim and/or the assailant: forced touching of genitals, forced oral sex, and forced vaginal or anal intercourse (and attempted intercourse).

An assault relationship was defined as all assaultive acts of a specific type (physical assault as a child, physical assault as an adult, sexual assault as a child, or sexual assault as an adult) that the patient experienced with a specific assailant, without regard for number of episodes or duration of relationship. Physical assault as an adult, for example, could range from being hit with a fist once to having been beaten up on many occasions over a period of years.

Each of the four assault types was inquired about separately. The interviewer used the appropriate assault scale as a probe to ask about possible assault relationships. A maximum of four assault relationships per assault type were described according to occurrence of each level of assault on the assault scale. Experiences before the age of 16 were classified as childhood experiences. In the inquiry regarding physical assault as a child, fighting that was "normal kid stuff," as determined by patient and interviewer, was excluded. Similarly, consensual sexual activity between children of similar ages was excluded from the category of sexual assault as a child.

One assault relationship of each type was examined further by using a detailed series of questions, such as the relationship with the assailant, alcohol or drug use, involvement of other family members, maintenance of secrecy about the assault, discussion of assault in previous therapy, and perceived effects of the assault. If a patient had experienced more than one assault relationship of a given type, one assault relationship was chosen by the patient as "the most important" for the more detailed inquiry.

Two medical students were trained by one of us (A.J.) and closely supervised during data gathering. Subjects and interviewers were matched for gender.

Patients were referred by the ward staff when they were considered stabilized enough to participate in the interview. The interviewer specified the subject matter

of physical and sexual assault and obtained informed consent. Interviews were held in private rooms and took 15–75 minutes, depending on the amount of history elicited. Demographic data were obtained first. The inquiry regarding physical assault as a child was followed by inquiries regarding physical assault as an adult, sexual assault as a child, and sexual assault as an adult. Interviews were well tolerated. All subjects had access to ward therapists after the interviews.

Patients were interviewed as close to discharge as possible to decrease the likelihood of obtaining delusional material; the median number of days before discharge for the interviews was 3–4 days. Attention was paid to face validity of each interview. The specificity and structure of the detailed inquiries about interpersonal circumstances tested the patient's capacity to give a very detailed account of the assault, and the length of the inquiry permitted evaluation of responses for internal consistency. Thirteen interviews were discarded because of vagueness, hostile denial of all inquiries, or apparent inconsistencies. Because of both confidentiality and concern for patients' safety, no attempts were made to obtain confirmatory data from other sources.

#### **RESULTS**

Major physical and/or sexual assault history was reported by 81% of the patients. Among the 81 subjects who had experienced major assault, 49 (60%) had experienced two or more different types of assault. Eighteen (22%) had experienced either three types or all four types.

Prevalence rates were calculated for each of the four major types of assault by gender and for the entire sample (table 1). Some patients reported more than one type of abuse. The combined prevalence of childhood physical and/or sexual assault was 57%; the prevalence of adult physical and/or sexual assault was 67%. The combined prevalence for childhood and/or adult physical assault was 76%. The prevalence of childhood and/or adult sexual assault was 35%. The only significant gender difference in prevalence rates was for a history of sexual assault as an adult, reported by 38% of the women but only 4% of the men (table 1).

The four types of major assault were analyzed in pairs for occurrence in the same patients by using corrected chi-square analyses. Physical assault as an adult and sexual assault as an adult tended to occur together among women patients ( $\chi^2$ =4.11, df=1, p<.05). However, this is largely accounted for by adults in relationships that involved both physical and sexual assault, and not by adult women experiencing physical and sexual assault with different assailants. There was a trend for patients who experienced physical assault as an adult ( $\chi^2$ =3.68, df=1, p<.10). No other significant associations were noted, either by gender or for the entire sample.

TABLE 1. Prevalence of Four Types of Major Assault Reported by 100 Psychiatric Inpatients

The second secon	Wor (N=			en =50)	Total (N=100)	
Type of Assault	N	%	N	%	N	%
Physical abuse as a child	22	44	27	 54	49	49
Physical abuse as an adult	32	64	31	62	63	63
Sexual abuse as a child	11	22	8	16	19	19
Sexual abuse as an adult	19ª	38	2	4	21	21

<sup>&</sup>lt;sup>a</sup>Significantly more women than men ( $\chi^2=15.42$ , df=1, p<.01).

The prevalence of certain circumstances of assault and certain perceived effects of assault among the 81 patients who had experienced major assault are presented in table 2. Among the 40 patients who said the assault had major effects on their current functioning, the majority of the effects were negative, such as decreased self-esteem and avoidance of sexual relationships. A few reported increased self-reliance or efforts not to abuse their own children. Although substantial numbers of each type of assault had gone unrevealed, men's experiences of sexual assault as a child were particularly likely not to have been revealed to anyone: five of the eight men who had experienced such assault had never revealed it to anyone; two of the three men who had previously revealed it had not done so in previous therapy. At the time of the interview, 16 of the patients who had been assaulted in any way said they had some kind of permanent physical damage or scar from an assault.

Seventy-seven relationships involving physical assault as a child were reported (some patients reported more than one such relationship). The majority of assailants (43 of 77, or 53%) lived in the same home as the assaulted patient. Similarly, the majority of assailants involved in physical assault as an adult (female victims only) (25 of 45, or 56%) shared the home with the victim. A minority of the assailants involved in the other types of assault—physical assault as an adult (male victims only) (12 of 53, or 23%), sexual assault as a child (four of 23, or 17%), and sexual assault as an adult (six of 26, or 23%)—lived in the home. Assaults in institutions were not separately tabulated.

#### **DISCUSSION**

Eighty-one percent of the patients interviewed reported at least one major assault experience. The prevalence for each of four specific subtypes of assault ranged from 19% to 63%. The prevalence rates found in this study are substantially higher than those suggested in the literature. Carmen et al. (7), for example, reported an overall prevalence of assault experience of 43%. Their prevalence rates for combined childhood and adult sexual assault and for combined adult and childhood physical assault were also approximately half of the prevalence rates noted here.

We suspect that part of the reason our prevalence

TABLE 2. Specific Characteristics of Major Assaults Reported by 81 Psychiatric Inpatients

	Patients Reporting Characteristic <sup>a</sup>			
Characteristic	N	%		
Occurred within 3 years before current				
hospitalization	39	48		
Lasted at least 2 years	36	44		
More than 20 episodes	40	49		
Involved a male assailant	78	96		
Involved a female assailant	20	25		
Alcohol or drug used by assailant,				
patient, or both <sup>b</sup>	41	51		
Caused major guilt or shame at time of				
occurrenceb	53	65		
Was never revealed to anyone <sup>b</sup>	22	27		
Was not revealed to previous therapists <sup>b</sup>	40	49		
Still causes major guilt or shame <sup>b</sup>	16	20		
Has major effect on patient's current life,	~~			
according to patientb	40	49		

<sup>a</sup>Each patient had experienced at least one major assault with the specified characteristics.

bSince only a subset of major assault was examined with respect to these characteristics, these data underestimate the total prevalence of exposure to assault with these characteristics.

figures are so high is that patients were asked directly about assault experiences. In many previous studies, chart review data were used. Since most clinicians do not routinely inquire about assault, charts mention only those assaults which the patient spontaneously discusses or, occasionally, that collateral sources describe. Assaults that patients are hesitant to discuss are usually missed. Also, our severe assault scales included some patients that other studies excluded. For example, completed intercourse, attempted intercourse, and forced genital contact were included in our major sexual assault scale, whereas other studies included only completed intercourse (5) or did not specify the severity of sexual assault reported.

Interviews were conducted by medical students, whose interviewing skills, compared with psychiatrists', are limited. The structure of the interview tended to reduce false-positive histories, as did careful review of the interviews by one of us (A.J.). However, any false-negative history due to less expert elicitation of sensitive history went undetected. For example, the very low prevalence of adult sexual assault acknowledged by male patients might have been higher if the interviews had been conducted by experts. Thus, the overall effect of using medical student interviewers was probably to underestimate the true prevalence of assault history.

The prevalence rates reported here refer only to major assaults. There were also other assault experiences that appeared very important psychologically but were not classified by our scales as major. A wife who had been repeatedly threatened, slapped, and shoved and had watched her husband slam his fist through the wall when angry at her would not have been classified as having experienced major physical assault, even though those events may have had a

profound effect both on the dynamics of the marriage and her own self-esteem. The prevalence figures would have been even higher had such "non-major" assaults been included.

We screened out assaults that seemed less important, even when they met the criteria for severity—e.g., mutually initiated barroom fights. The remaining major assaults varied in severity. One episode of being forced to touch an uncle's penis, however undesirable, is likely to have less effect than repeated forced intercourse over a period of years. However, many of the experiences reported involved multiple assaults and long durations rather than single episodes. And even single episodes of assault may have pivotal effects, either on the dynamics of the relationship in which they occur or on the victim's future relationships.

The prevalence rates reported among psychiatric patients are substantially higher than available prevalence estimates for the general nonpsychiatric population. The lifetime prevalence of major marital violence has been estimated at about 13% in a study using the physical assault scale from which ours was drawn (1). The prevalence of inappropriate childhood sexual encounters, excluding exhibitionism, has been estimated to be 15% among women (2). There are no adequate studies of the prevalence of rape, but a prevalence of 9% (14% among women who have ever been married) has been reported for marital rape (11). We are aware of no estimates of prevalence in the general population of any of the four types of assault that approach the prevalence rates reported here. Thus, assault experiences appear to be a greater problem among psychiatric patients. This interpretation, however, remains tentative until the same interview is used in a normal population.

The population sampled was an inpatient population with severe diagnoses. An outpatient population with less severe diagnoses may have lower prevalence rates of assault history. The effects of both severity of diagnosis and social class are now being examined by repeating this study in a middle-class outpatient sample.

In addition to establishing high prevalence rates, the data obtained provide several kinds of evidence that assault experiences are relevant to current psychiatric treatment. Many patients had experienced assault within a few years before hospitalization. Substantial guilt and shame had been associated with the assault and for some patients still remained. Patients often reported that the assault continued to have an important effect on their current functioning, and a significant minority carried physical scars as reminders of the assault. For some, the assaults had remained secret from family and friends and also from previous therapists.

The data discussed here support the importance of routine inquiry. Routine inquiry can elicit an assault history that has been previously hidden and that may be useful for understanding the patient's development. Furthermore, the history is often seen by the patients as being important. By asking, the clinician demonstrates that he or she too believes that such history is

important, and by listening to assault history when it is elicited, the clinician demonstrates his or her capacity to understand and tolerate painful events from the patient's past. The patient's experience of these capacities in the clinician is central to a therapeutic alliance and effective treatment.

Patients who were assaulted during childhood by parents or other adults in authority have experienced the subversion of a hierarchical relationship intended to nurture and teach them into a relationship that served the aggressive or sexual needs of the adult. When these patients enter therapy, they are once again entering a hierarchical relationship intended to benefit them. However, their previous experience suggests the possibility that the therapeutic relationship will be used instead to serve the therapist's aggressive or sexual needs. Obtaining the assault history early in treatment alerts the therapist to the possibility of this transference. Errors such as mistaking a patient's persistent wariness for an inability to establish a therapeutic alliance may thereby be avoided.

Since experience with male assailants is far more prevalent than with female assailants (78% versus 20%), male therapists should be particularly alert to the possibility of being viewed as a potential assailant. Female therapists may experience transference of anger that was felt toward a mother who did not (or could not) protect the patient from assault. When patients were assaulted by a woman, the possible transferences may be reversed.

The high prevalence of alcohol or drug use by the assailant and/or the victim (51%) suggests the value of careful inquiry into alcohol or drug use when a history of assault is revealed and into a possible history of assault if alcohol or drug abuse is present.

Marital dynamics may also be clarified by obtaining a history of assault. A difficult sexual adjustment is better understood if the clinician is aware that one of the partners was sexually assaulted as a child. A wife who "can't" learn to disagree openly is less puzzling once it is known that she has been physically assaulted by her husband.

It would be most helpful to be able to specify the effects of assault and its relation to later development of psychopathology. Retrospective studies have examined the effects of assault (12–14). Prospective studies, however, are needed to fully specify the effects of assault and to guide intervention attempts. The data reported here examine the effects of assault only by demonstrating the importance attributed to the assaults by the patients. Forthcoming articles, specific to each assault type, will examine these data for correlations between various circumstances of assault, diagnosis, and perceived outcome.

Meanwhile, the high prevalence of assault history, the patient's perceptions of the assaults as important, retrospective studies of the effects of assault, and the possible effects of the assault history on the therapeutic relationship all indicate that the effort of routine inquiry about assault history is justified.

#### ROUTINE INQUIRY ABOUT ASSAULT HISTORY

Different patient populations and interview circumstances will determine how and when assault inquiry is conducted. However, a few general suggestions can be offered.

- 1. Develop routine times and routine ways to ask about each type of assault. Physical assault as a child can be inquired about during childhood history taking, using questions such as, What was the worst punishment you ever received? and Were you ever hurt physically as a child? Physical assault as an adult can be explored during a discussion of marital function and decision making, e.g., What happens when you disagree? Does either of you get angry enough to hit or threaten the other? Inquiry regarding sexual assault as a child can be a question such as, When you were a child, did anything sexual ever happen that made you uncomfortable? Or worries you now? Sexual assault as an adult can be approached by asking, Have you ever felt forced to be sexual with anyone, including your mate? A general question such as, Have you had any (other) experiences of being hurt physically, or forced into sexual activity? can elicit additional history. Once these questions are familiar to the therapist, they take very little time to ask.
- 2. Ask about the circumstances and perceived effects of the assault. How long did the assault go on? What were the patient's feelings about the assault at the time? (Sexual assault as a child may not have been perceived as an assault, in which case the clinician should not impose the word "assault.") Was anyone else told, and how did they respond? What ended the assault? What does the patient think are the current effects of the assault, if any?
- 3. Be able to ask about specific levels of assault. When a patient says her mother's boyfriend "messed with her," the clinician needs to be comfortable asking for details or, when appropriate, describing different levels of assault for the patient to confirm or disconfirm. The clinician's need to obtain objective details must, however, be balanced by respect for the patient's timing in discussing these difficult experiences.
- 4. Test the usefulness of routine inquiry. Just as the general medical doctor may not be accustomed to inquiring comfortably about suicide attempts, most psychiatrists have not been trained to inquire comfortably about experiences of physical and sexual assault. Experience with routine inquiry is the best solution to this difficulty. It is also the only way in which the individual clinician can determine whether this inquiry is fruitful in his or her own practice.

#### **REFERENCES**

- Straus MA, Gelles RJ, Steinmetz SK: Behind Closed Doors: Violence in the American Family. New York, Anchor/ Doubleday, 1980
- Herman JL: Father-Daughter Incest. Cambridge, Harvard University Press, 1981

- 3. Kempe CC, Helfer RE: Preface, in The Battered Child, 2nd ed. Edited by Kempe CC, Helfer RE. Chicago, University of Chicago Press, 1980
- 4. Lukianowicz N: Incest, I: paternal incest. Br J Psychiatry 1972; 120:301-313
- 5. Rosenfeld AA: Incidence of a history of incest among 18 female psychiatric patients. Am J Psychiatry 1979; 136:791-795
- 6. Husain A, Chapel JL: History of incest in girls admitted to a psychiatric hospital. Am J Psychiatry 1983; 140:591-593
  7. Carmen E(H), Rieker PP, Mills T: Victims of violence and
- psychiatric illness. Am J Psychiatry 1984; 141:378-383
- 8. Straus MA: Measuring intrafamily conflict and violence: the Conflict Tactics (CT) Scales. J Marriage and the Family 1979;

- 9. Finkelhor D: Sexually Abused Children. New York, Free Press. 1979
- 10. Tsai M, Feldman-Summers S, Edgar M: Childhood molestation: variables related to differential impacts on psychosexual functioning in adult women. J Abnorm Psychol 1979;
- 11. Russell DEH: Rape in Marriage. New York, Collier, 1982
- 12. Herman J, Russell D, Trocki J: Long-term effects of incestuous abuse in childhood. Am J Psychiatry 1986; 143:1293-1296
- 13. Gelinas D: The persisting negative effects of incest. Psychiatry 1983; 46:312-332
- 14. Egeland B, Sroufe LA, Erickson M: The developmental consequence of different patterns of maltreatment. Child Abuse Negl

### Shifts in Attitudes Among Psychiatric Residents: Serial Measures Over 10 Years

William Coryell, M.D.

Psychiatric residents completing their training in 1976, 1978, 1980, and 1986 were sent surveys on their attitudes toward treatment and training among a "dynamic-organic continuum." Their responses indicated decreasing antagonism toward the medical model and increasing endorsement of medical education, experience in neurology, and the internship as essential aspects of psychiatric education. The rankings of various treatment modalities for each of four disorders were remarkably stable across surveys. Except for megavitamin therapy, residents in 1986 were at least somewhat more likely to consider essential each of six therapies for each of the four disorders, indicating a general increase in therapeutic optimism. (Am J Psychiatry 1987; 144:913–917)

The advents of effective pharmacotherapy, operationally defined diagnoses, and new biological probes suggest that American psychiatry is gathering a firmer scientific base or perhaps even undergoing a "biological revolution" (1). Concurrently, increasing numbers of nonphysician psychotherapists are com-

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peting with psychiatrists, and many expect this competition to force psychiatrists to emphasize those services that are unique to physicians and thus to focus on the diagnosis and biological treatment of the more severe psychiatric illnesses. Although these changes are frequently the subject of discussions at psychiatric meetings, there have been few efforts to systematically measure their impact on prevailing attitudes among psychiatrists.

The study described here exploited a unique opportunity to do this. In response to several articles noting hostility toward the medical model approach among at least some residents (2, 3), in 1976 I undertook a nationwide survey of psychiatric residents in their final years of training (4). The results revealed widespread appreciation for biological treatment and little outright rejection of the medical model in psychiatry. Two identical surveys followed at 2-year intervals and revealed little change in these attitudes over the 4 years encompassed (5). Whatever change was taking place was apparently too gradual to manifest itself in 4 years. Therefore, 6 years elapsed before the next survey, and a total of 10 years was covered by the serial mailings.

#### **METHOD**

Identical surveys were mailed in the winters of 1976, 1978, 1980, and 1986 to one-half of all psychiatric residents completing their final year in approved

1976 (N = 378)

1978 (N = 315)

1980 (N = 252)

1986 (N = 308)

FIGURE 1. Aspects of Psychiatric Education Considered Essential by Residents Surveyed From 1976 to 1986

**Analysis** 

ASPECT OF PSYCHIATRIC EDUCATION

Pharmacotherapy

Clinical

Experience in

Neurology

<sup>a</sup>p<.007, Kendall's tau.

Medica!

Educationa

American programs. The questionnaire, described in more detail elsewhere (4, 5), was designed to assess attitudes along a "dynamic-organic continuum" (6) and to be as brief as possible to enhance response. The need for maximum return rates counterbalanced the need for comprehensive assessment, and since it was predicted that only an atypical sample of residents would tolerate a lengthy survey, the questionnaire was designed to be completed within 3 minutes.

Training in

Psychoanalysis

The residents were first asked to rate various aspects of training as "essential," "desirable but not essential," or "of no value." They then selected the "form of individual non-biological (non-organic) therapy" they preferred "for the majority" of their patients from a brief list that included psychoanalytic psychotherapy and behavior therapy. Then, for each of four illnesses-chronic (poor-prognosis or process) schizophrenia, acute (good-prognosis) schizophrenia, endogenous depression, and alcoholism—the residents rated the values of individual psychotherapy, milieu therapy, organic therapy, behavior therapy, group therapy, and megavitamin therapy. Next they endorsed one of three statements regarding the medical model in psychiatry. Finally, they designated their career plans and institutional affiliation.

The nonparametric rank-ordered correlation coefficient Kendell's tau was chosen to test the differences in ratings across surveys. To correct for the number of statistical tests performed, the conventional p value of .05 was divided by 7 for the analysis of aspects of psychiatric education and by 24 for the treatment sections (six tests were performed for each of the four diagnoses). Thus, changes over the surveys were considered significant only if the p value was less than .007 in the first or .002 in the second group of analyses. To qualify as a meaningful trend, a change was required to be not only statistically significant at the assigned level but also uniform—that is, consistently unidirec-

tional. Finally, a repeated measures linear model analysis was used to determine the extent to which the survey year (the passage of time) determined the responses to treatment questions beyond the effects of diagnosis and treatment modality.

Research

Experience

Internship<sup>a</sup>

#### **RESULTS**

In 1976, 1978, 1980, and 1986, surveys were delivered to 698, 642, 658, and 635 residents, respectively. Of these, 53.4%, 49.1%, 38.3%, and 48.5% returned the surveys. This represents a highly significant ( $\chi^2$ = 33.1, df=3, p<.0001) but unexplained fluctuation in response rates. Essentially, no descriptive data are available for the nonrespondents; they may or may not have resembled the respondents in relevant ways.

Consistently increasing proportions of residents considered medical education, clinical experience in neurology, and the internship essential to psychiatric education (figure 1). Of these, by far the greatest gains were found for the internship; residents in 1986 were almost twice as likely to consider this essential to their training as were residents in 1976. Likewise, residents increasingly viewed experience in neurology as highly important. Medical education and pharmacotherapy were almost universally endorsed with the first survey, but the consensus grew nevertheless. Notably, no coherent trends in either direction emerged for training in psychoanalysis or for the personal analysis or psychotherapy of the individual resident. Experience in research remained by far the least likely to be considered essential.

More of the residents in 1986 than in 1976 endorsed as "essential to successful treatment" each of the six forms of therapy for all four illnesses (figures 2–5). Of the 24 possible changes, there were no exceptions to this general increase in enthusiasm, although most of

1976 (N = 378)RESIDENTS RATING MODALITY ESSENTIAL (%) 1978 (N = 315)1980 (N = 252) 1986 (N = 308) JOZOZIL Individual Milieu Behavior Organic Group Megavitamin Psychotherapy Therapy Therapy Therapy Therapy Therapy

TREATMENT MODALITY

FIGURE 2. Treatment Modalities Considered Essential for Acute (Good-Prognosis) Schizophrenia by Residents Surveyed From 1976 to 1986

<sup>a</sup>p<.002, Kendall's tau.

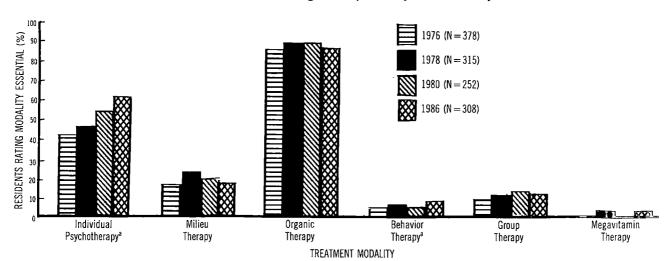


FIGURE 3. Treatment Modalities Considered Essential for Endogenous Depression by Residents Surveyed From 1976 to 1986

ap<.002, Kendall's tau.

the changes were statistically insignificant. A repeated measures linear model indicated a highly significant year effect (F=3.94, df=3, 1182, p<.0001) after controlling for both diagnosis and treatment type.

The following modalities met the stated criteria for meaningful trends in the proportion of residents rating them as essential: organic therapy (chemotherapy or ECT) for acute schizophrenia, individual psychotherapy for endogenous depression, and group therapy for alcoholism. There were no meaningful trends for chronic schizophrenia, although several of the modalities (e.g., individual psychotherapy and milieu therapy) were considered essential by slightly more residents in 1986 than in 1976. Also in 1986, as in the first three surveys, organic therapy was more than twice as likely as any other therapy to be regarded as essential

for chronic schizophrenia.

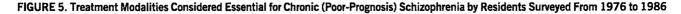
In all four surveys a minority of residents selected psychoanalytic psychotherapy as their preferred form of nonbiological therapy. Serial measures showed no trend toward increasing or decreasing popularity for this approach to psychotherapy. Likewise, the popularity of behavioral therapy did not change; in 1976, 4.6% of residents selected this mode, while in 1986, 5.8% did so.

Although the proportion of residents who endorsed the medical model as basic to psychiatry showed no meaningful trend over these four surveys (table 1), the proportions indicating an essentially negative attitude showed a steady decrease. The percentages checking either the second or third statement in table 1 were 26.0%, 20.9%, 19.5%, and 16.8% for the survey

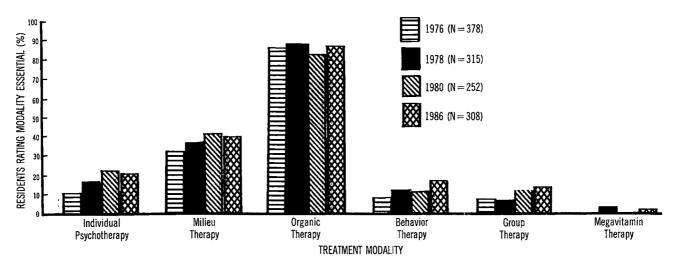
1976 (N = 378) 8 RESIDENTS RATING MODALITY ESSENTIAL 1978 (N = 315) 1980 (N = 252)1986 (N = 308) Megavitamin Behavio Group Milieu Organic Individual Therapya Therapy Therapy Therapy Psychotherapy Therapy

FIGURE 4. Treatment Modalities Considered Essential for Alcoholism by Residents Surveyed From 1976 to 1986

<sup>a</sup>p<.002, Kendall's tau.



TREATMENT MODALITY



years 1976, 1978, 1980, and 1986, respectively ( $\chi^2$ =10.9, df=3, p<.025).

Career aspirations apparently changed little over the survey years. In 1986, as in 1976, roughly one in five (20.5% and 22.3%, respectively) residents intended a career in academic psychiatry. On both occasions roughly twice as many (44.2% and 41.0%, respectively) planned private practice.

#### DISCUSSION

These survey results are perhaps most striking for their stability across surveys. There was, for instance, essentially no change in the ranking of various educational aspects; in all four surveys a medical education and training in psychopharmacology were most often considered essential, followed by experience in neurology and then by the internship. The respondents to all of the surveys were least likely to consider research experience essential. Despite substantial variations in treatment ratings by diagnosis, the patterns here were also remarkably consistent across the years surveyed.

Are attitudes changing to reflect a growing medical base for American psychiatry? The psychiatric education ratings indicate so, as do the responses to the medical model statements. In most cases these trends were too subtle to emerge over 4 years and became clear only with the final, 10-year survey.

Interpretation of the treatment ratings is more difficult. First, the ratings for "organic therapy" were quite high with the first survey, leaving little room for increases in endorsements. Second, an unexpectedly general increase in enthusiasm emerged, displaying itself in five of the six treatment modalities in all four of the diagnostic categories. These surveys, of course, cannot identify a source for this apparently indiscriminate increase in therapeutic optimism. However, since

TABLE 1. Attitudes Toward the Medical Model in Psychiatry Among Residents Surveyed From 1976 to 1986

	Respondents Endorsing Statement									
	1976 (N=371)				1980 (N=249)			986 =308)		
Attitude	N	%	N	%	N	%	N	%		
The medical model should be basic to both the practice of and research in psychiatry  The medical model has merit with some patients, but its usefulness and	215	58.0	209	66.8	147	59.0	208	67.5		
importance are minimal in psychiatry  The medical model has little meaning in psychiatry and its use may even be	89	24.0	59	18.8	45	18.1	50	16.2		
countertherapeutic None of the above	8 59	2.2 15.9	7 38	2.2 12.1	4 53	1.6 21.3	2 48	0.6 15.6		

an opinion that a treatment is essential implies necessarily an opinion that it is effective, psychiatrists about to begin their careers seem to be generally, if only somewhat, more confident that the various therapeutic tools they have available are in fact helpful.

#### REFERENCES

- Andreasen NC: The Broken Brain. New York, Harper & Row, 1981
- 2. Engel GL: Is psychiatry failing in its responsibilities to medi-

- cine? Am J Psychiatry 1972; 128:1561-1564
- Greden JF, Casariego JI: Controversies in psychiatric education: a survey of residents' attitudes. Am J Psychiatry 1975; 132: 270-274
- Coryell W, Wetzel RD: Attitudes toward issues in psychiatry among third-year residents: a brief survey. Am J Psychiatry 1978; 135:732-735
- Coryell W: The organic-dynamic continuum in psychiatry: trends in attitudes among third-year residents. Am J Psychiatry 1982; 139:89-91
- West LJ: The future of psychiatric education. Am J Psychiatry 1973; 130:521–528

### Which Mexican-Americans Underutilize Health Services?

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Data collected from the Los Angeles site of the National Institute of Mental Health Epidemiologic Catchment Area Program were used to examine the utilization of health services in a community population. Mexican-Americans, especially the less acculturated, had significantly lower rates of use of outpatient, but not inpatient, care than non-Hispanic whites. Differences were greater for mental than physical health care. Less acculturated Mexican-Americans made very little use of either mental health specialists or the human services sector (e.g., religious leaders). Among those with a recent psychiatric disorder, non-Hispanic whites were seven times more likely to use outpatient mental health services than the less acculturated Mexican-Americans.

(Am J Psychiatry 1987; 144:918–922)

By the year 2000, the Hispanic-American population is expected to be the nation's largest ethnic group (1). The 1980 U.S. census estimate of this population is 14.6 million, probably a conservative figure; the majority are of Mexican descent. At major points of immigration, especially in the southwestern states, the delivery of health care to Mexican-Americans is a major clinical and policy concern (1, 2).

There has been much speculation and some data suggesting that Mexican-Americans underutilize health services (3–8). A previous examination of data from the Los Angeles site of the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program indicates that Mexican-Americans are less likely than non-Hispanic whites to report outpatient general health or mental health care but have a

similar probability of a medical hospitalization (9). It has not been clear, however, whether underutilization is limited to Mexican-Americans who are less acculturated (e.g., those who do not speak English). Further, it is unclear whether the Mexican-Americans who most need care—those with serious clinical problems—underutilize health services, compared to similar non-Hispanic whites. If so, the importance of developing health care programs for this rapidly growing population is enhanced.

Mexican-Americans who have less fully adopted the predominant U.S. (Anglo) culture could have an especially low level of use of health services, for several reasons. First, they may be unacquainted with the available services or may experience language difficulties or other problems, such as difficulty obtaining transportation or child care, that interfere with receiving medical care (5, 6, 8, 10, 11). Second, the less acculturated may make greater use of alternative systems of care, such as folk practitioners (6, 10). Third, they may have low incomes or lack health insurance coverage (3, 5, 6, 10).

Mental health services may be especially underutilized by less acculturated Mexican-Americans. Areas of Mexico that border on the United States have few mental health professionals; recent immigrants from these areas may be unfamiliar with such providers. In addition, the available services may be oriented to the perceived mental health needs of middle and upper socioeconomic class whites and less appropriate for the needs of less acculturated Mexican-Americans. Language differences may be especially strong deterrents to the use of mental health care because verbal communication is so central to treatment. Finally, less acculturated Mexican-Americans may attach a greater stigma to mental illness. While several authors have presented arguments that support these hypotheses, there are few available data (5, 8-10).

In the relatively few previous studies of acculturation and use of health services, the role of health status and level of acculturation in explaining underutilization of Mexican-Americans is unclear. Vernon and Roberts (12) observed similar rates of use of mental health specialists for non-Hispanic whites and Mexican-Americans who had a psychiatric disorder. Griffith (13), however, after controlling for psychological distress, found much lower rates of use of mental health

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services for Mexican-Americans than non-Hispanic whites. Markides et al. (14) found only small differences in use among Mexican-Americans on the basis of level of acculturation. The discrepancies in conclusions from the studies must be resolved before policies can be developed that address the health care needs of Mexican-Americans.

In this paper, we examine rates of health service utilization for Mexican-Americans of low and high acculturation and compare these rates with those for non-Hispanic whites, using data from the Los Angeles Site of the NIMH Epidemiologic Catchment Area Program.

#### **METHOD**

The NIMH Epidemiologic Catchment Area Program is a multisite general population survey of the epidemiology of psychiatric disorders and use of health services (15–17). In the Los Angeles project site, staged probability samples of household residents from two mental health catchment areas (East Los Angeles and Venice/Culver City) were drawn. Approximately 50% of the respondents were of Hispanic origin (mostly Mexican-American) (8). This paper reports data obtained from face-to-face interviews with 3,132 community residents (a completion rate of 68%) conducted in 1982 and 1983.

The interviews elicited information on sociodemographic characteristics, general health status, use of health services, and presence or absence of specific psychiatric disorders.

Data on psychiatric disorders were obtained with the NIMH Diagnostic Interview Schedule (DIS), a structured interview administered by lay persons that yields diagnoses according to *DMS-III* criteria (18). A Spanish-language version of this instrument was developed specifically for this study (19, 20). For the 6 months before the interview, we determined the presence of any or absence of all of the following: affective, anxiety, substance abuse, obsessive-compulsive, schizophrenia/schizophreniform, and somatization disorders; antisocial personality; and severe cognitive dysfunction.

The interview included 46 items assessing physical health and functional status in the previous 6 months. We developed an indicator variable for the presence or absence of any limitation in physical or role functioning due to physical health.

Mexican-Americans were identified by self-declared ethnic status; when this was ambiguous we used the parents' ethnic background and country of birth. The analyses reported here are limited to non-Hispanic whites and Mexican-Americans (82% of respondents).

Acculturation was measured by a 26-item scale (see references 21–23) that assesses language, food, entertainment, and social interaction choices. The scale's reliability and construct validity are excellent (M.A. Burnam et al., unpublished data). We contrasted Mex-

TABLE 1. Sex and Age Distribution of Mexican-American (N=1,243) and Non-Hispanic (N=1,309) Community Residents in a Survey of Use of Health Services

Sex and Age (years)	Mexican-	Americans	Non-Hispanic Whites			
	, N	%	N	%		
Men	591	100	631	100		
18-24	120	20	66	10		
25-44	312	53	339	54		
4564	109	18	138	22		
65+	50	8	88	14		
Women	652	100	678	100		
18-24	127	19	67	10		
25-44	304	47	341	50		
45-64	141	22	153	23		
65+	80	12	117	17		

ican-Americans above and below the median scale score (i.e., high and low acculturated).

The interview elicited data on the number of outpatient visits for mental and physical health problems in the 6-month period before the interview. Respondents also indicated the number of hospitalizations or overnight stays for mental and physical health reasons in the 12 months before the interview.

We grouped providers of mental health services into specialty mental health (e.g., psychiatrists, psychologists), general medical (e.g., nonpsychiatrist physicians), and human service (e.g., family or social services, self-help groups, clergy) (see reference 24).

We used cross-tabulations to compare use of services for non-Hispanic whites, as a group, with low-and high-acculturated Mexican-Americans, while controlling for the presence or absence of either physical limitations or psychiatric disorders. Means and percentages were adjusted for sex and age, and non-Hispanic whites were used as the reference group. Because only one adult was interviewed in each household, we weighted analyses by the number of adults in each household. Data were also weighted to adjust for differential probability of selection across the two catchment areas. Significance tests and standard errors were corrected for the staged sampling design (i.e., they approximate exact variance estimates) (25).

#### **RESULTS**

The full sample included 2,552 non-Hispanic whites and Mexican-Americans. Table 1 provides age and sex distributions by ethnicity. The analytic sample for this paper consisted of 1,309 non-Hispanic whites and 1,194 Mexican-Americans; we excluded 49 Mexican-Americans who had missing data on one or more study variables.

As shown in table 2, age- and sex-adjustment rates of hospitalization for physical health problems in a 1-year period were similar for non-Hispanic whites and both high- and low-acculturated Mexican-Americans. For each group, hospitalization rates were 2½ to 3½ times higher for those with than for those without

TABLE 2. Relationship Between Acculturation, Health Status, and Use of Health Services for Physical and Emotional Problems by Non-Hispanic Whites (N=1,309) and Mexican-Americans With High (N=598) or Low (N=596) Acculturation

	Percent of Group (adjusted for age and sex)								
			Mexican-Americans						
	Non-Hispanic Whites		High Acculturation		Low Acculturation				
Type of Use	Mean	SE	Mean	SE	Mean	SE			
Treatment for physical problems									
Hospitalization in previous 12 months									
All respondents	9.8	0.8	10.4	1.5	9.1	1.0			
With physical limitation	19.4	2.4	23.7	5.0	20.2	4.6			
Without physical limitation	7.9	0.8	7.2	1.2	7.2	1.0			
With psychiatric disorder	12.8	2.2	13.6	2.6	9.2	3.0			
Without psychiatric disorder	9.3	0.8	9.7	1.7	8.9	1.0			
Outpatient visit in previous 6 months									
All respondents	55.4	1.4	40.9	2.2	36.3	2.1			
With physical limitation	72.3	3.1	59.0	4.8	69.2	5.1			
Without physical limitation	52.3	1.6	35.6	2.5	32.2	2.1			
With psychiatric disorder	64.3	4.0	47.3	4.7	40.2	4.0			
Without psychiatric disorder	53.2	1.6	38.7	2.4	35.6	2.1			
Outpatient treatment for emotional									
problems in past 6 months									
General medical sector									
All respondents	2.6	0.5	2.0	0.5	2.2	0.7			
With physical limitation	5.3	1.4	2.7	1.1	4.0	2.1			
Without physical limitation	2.1	0.6	1.9	0.7	1.5	0.7			
With psychiatric disorder	6.8	1.4	2.2	1.3	6.1	2.3			
Without psychiatric disorder	1.8	0.6	2.1	0.6	1.2	0.6			
Specialty mental health									
All respondents	7.8	0.6	4.2	0.8	1.1	0.6			
With physical limitation	11.7	1.9	6.9	3.0	5.0	2.9			
Without physical limitation	7.2	0.7	3.8	0.8	0.4	0.2			
With psychiatric disorder	16.0	2.1	11.3	2.6	3.1	1.8			
Without psychiatric disorder	5.6	0.7	1.8	0.7	0.6	0.3			
Human service sector									
All respondents	6.0	0.7	3,9	0.9	1.0	0.4			
With physical limitation	9.4	2.0	5.3	2.9	2.3	2.3			
Without physical limitation	5.2	0.7	3.2	0.8	0.9	0.5			
With psychiatric disorder	10.9	1.9	5.5	1.9	1.1	0.8			
Without psychiatric disorder	4.7	0.9	3.8	1.1	1.0	0.5			

a physical limitation. Psychiatric disorder had little effect on these rates. There were no reported psychiatric hospitalizations in any of the groups for the 1-year period.

Both high- and low-acculturated Mexican-Americans were less likely to have had an outpatient visit for physical health reasons in the past 6 months than were non-Hispanic whites (t=5.77, df=1,905, p<.001, and t=7.58, df=1,903, p<.001, respectively). Differences between the two groups of Mexican-Americans were not marked and were not statistically significant.

There were no significant or appreciable differences among the three groups in the percent using the general medical sector for emotional problems; from 2% to nearly 3% of each group had had such a visit in the past 6 months (table 2). Among those with a psychiatric disorder, however, non-Hispanic whites were three times as likely to have had such a visit as the high-acculturated group (t=2.39, df=1,905, p<.05); the percent for the low-acculturated group was not significantly different from that for either the non-Hispanic white or the high-acculturated group. This interaction effect was not statistically significant when

we also controlled for socioeconomic status and other individual characteristics through regression analysis.

Non-Hispanic whites were nearly twice as likely as the highly acculturated Mexican-Americans (t=3.63, df=1,905, p<.01) and nearly seven times as likely as the low-acculturated Mexican-Americans (t=8.28, df=1,903, p<.0001) to have made a visit to the mental health specialty sector in the past 6 months (table 2). Similar differences occurred among those with a recent psychiatric disorder.

Among those with a psychiatric disorder, age- and sex-adjusted rates of use of the human service sector (e.g., priests, folk practitioners) for emotional problems were twice as high for non-Hispanic whites as for highly acculturated Mexican-Americans (t=1.80, df=1,905, p<.10), who in turn had four times the rate of use of the low-acculturated group (t=2.88, df=1,192, p<.05). We observed similar results for those with a physical limitation.

There were no significant or appreciable differences among the three groups in mean visits per user for outpatient care for either physical or emotional health concerns.

With the exception noted earlier, the differences by ethnicity and acculturation reported here remained statistically significant in logistic regression analyses that controlled for sociodemographic and economic factors, health insurance status, psychiatric disorder, and physical limitations.

#### **DISCUSSION**

We found marked underutilization of health services by Mexican-Americans, particularly the less acculturated, in comparison with non-Hispanic whites. The differences were observed for outpatient rather than inpatient services and in the percent receiving care rather than in the intensity of care per user. Underutilization was greater for care of emotional than of physical problems. Thus, in this study, being Mexican-American was associated with low rates of entry into outpatient care, particularly psychotherapy. These differences remained even after we controlled for clinical status (i.e., recent psychiatric disorder and physical limitations), sex, and age. Thus, lower use by Mexican-Americans was not due to better health status; rather, unfamiliarity with services or other barriers to care, such as lack of health insurance, are likely explanations.

Non-Hispanic whites were more likely to report a general medical visit for physical health problems than either group of Mexican-Americans. These results suggest that Mexican-Americans are less likely than non-Hispanic whites to receive services for health promotion or minor physical problems. We did not observe a parallel pattern among Mexican-Americans as a function of acculturation. Our finding is consistent with the conclusion of Andersen et al. (3) that Hispanic-Americans have a lower rate of use of preventive services than non-Hispanic whites.

Only about 1% of the less acculturated Mexican-Americans had any care from the mental health specialty sector. The less acculturated may be especially unfamiliar with formal mental health services or especially reluctant to use them. For the low-acculturated Mexican-Americans, use of this sector was higher (but not significantly so) among those with a physical limitation than among those with a psychiatric disorder. For non-Hispanic whites, in contrast, such use tended to be higher among those with a psychiatric disorder than among those with a physical limitation. For the less acculturated Mexican-Americans, physical limitations may be perceived as a "legitimate" reason for seeking care; alternatively, physical limitations may increase referral from the general medical sector to mental health specialists.

Less acculturated Mexican-Americans with a recent psychiatric disorder were twice as likely to receive mental health care from a general medical provider as from a mental health specialist. By contrast, both more acculturated Mexican-Americans and non-Hispanic whites with psychiatric disorders were more likely to visit a mental health specialist. The relatively greater

reliance of less acculturated Mexican-Americans on general medical providers for mental health care may reflect greater familiarity with these providers, financial or other barriers to mental health specialty care, or a tendency to perceive psychiatric symptoms as an indication of a physical health problem. Regardless of the explanation, general medical providers appear to be an especially important source of mental health care for the Mexican-Americans in this study; this finding enhances the importance of training these providers to recognize psychiatric disorders in Mexican-Americans.

Despite speculation that less acculturated Mexican-Americans use the human service sector in lieu of formal mental health care, these respondents had a much lower rate of use of this sector than either the high-acculturated group or the non-Hispanic whites. This is an important and unexpected finding. It means that the less acculturated Mexican-Americans are less likely to have contact with any formal support services. This finding further enhances the role of the general medical provider as the point of entry for care.

Our estimates of the use of outpatient mental health services in the past 6 months for non-Hispanic whites were at the upper range of estimates of annual use for the general U.S. population (26–28). Los Angeles, however, would be expected to have higher rates of use by virtue of the western location and sophistication of the medical marketplace (27, 29).

In sum, our results dramatically illustrate underutilization of health services by the less acculturated Mexican-Americans in Los Angeles, even among those with current psychiatric disorders and limitations in functioning due to physical health. Lower rates of use were not explained by differences in the prevalence of serious clinical problems or by differences in reliance on alternative sources of care, such as folk practitioners. For areas such as Los Angeles, it seems especially appropriate to develop programs that address the mental health needs of less acculturated Mexican-Americans and to train providers at points of entry for health care for this population to recognize psychiatric disorders.

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- Macias RF: US Hispanics in 2000 AD—projecting the number. Agenda 1977; 7:16–20
- Trevino FM, Moss AJ: Health Insurance Coverage and Physician Visits Among Hispanic and Nonhispanic People in the US National Center for Health Statistics. Washington, DC, US Government Printing Office, 1984
- 3. Andersen R, Lewis SZ, Giachello AL, et al: Access to medical care among the Hispanic population of the Southwestern United States. J Health Soc Behav 1981; 22:78–89
- Griffith J: Re-examination of Mexican American service utilization and mental health need. Hisp J Behav Sci 1983; 5:163

  180
- Lopez S: Mexican-American usage of mental health facilities: underutilization considered, in Explorations in Chicano Psychology. Edited by Baron A. New York, Praeger, 1981
- Padilla AM, Ruiz RA, Alvarez R: Community mental health services for the Spanish-speaking/surnamed population. Am Psychol 1975; 30:892-905
- Acosta FX: Barriers between mental health services and Mexican Americans: an examination of a paradox. Am J Community Psychol 1979; 7:503-520
- Hough RL, Karno M, Burnam MA, et al: The Los Angeles Epidemiologic Catchment Area Research Program and the epidemiology of psychiatric disorders among Mexican-Americans. J Operational Psychiatry 1983; 14:42–51
- 9. Hough RL, Landsverk JH, Karno M, et al: Utilization of health and mental health services by Los Angeles Mexican Americans and nonhispanic whites. Arch Gen Psychiatry (in press)
- Keefe SE: Mexican Americans' underutilization of mental health clinics: an evaluation of suggested explanations. Hisp J Behav Sci 1979; 1:93-115
- Barrera M: Mexican-American mental health service utilization: a critical examination of some proposed variables. Community Ment Health J 1978; 14:35–45
- Vernon SW, Roberts RE: Prevalence of treated and untreated psychiatric disorders in three ethnic groups. Soc Sci Med 1982; 16:1575-1582
- Griffith J: A community survey of psychological impairment among Anglo- and Mexican Americans and its relationships to service utilization. Community Ment Health J 1985; 21:28-41
- Markides KS, Levin JS, Ray LA: Determinants of physician utilization among Mexican-Americans: a three-generations study. Med Care 1985; 23:236-246
- Regier DA, Myers JK, Kramer M, et al: The NIMH Epidemiologic Catchment Area Program: historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984; 41:934–941

- Eaton WW, Holzer CE, Von Korff M, et al: The design of the Epidemiologic Catchment Area Surveys. Arch Gen Psychiatry 1984; 41:942–948
- Eaton WW, Kessler LG (eds): Epidemiologic Field Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program. Orlando, Fla, Academic Press, 1985
- Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981; 38:381

  389
- Karno M, Burnam MA, Escobar JI, et al: Development of the Spanish-language version of the National Institute of Mental Health Diagnostic Interview Schedule. Arch Gen Psychiatry 1983; 40:1183–1188
- Burnam MA, Karno M, Hough RL, et al: The Spanish Diagnostic Interview Schedule: reliability and comparison with clinical diagnoses. Arch Gen Psychiatry 1983; 40:1189–1196
- Cuellar I, Harris LC, Jasso R: An acculturation scale for Mexican American normal and clinical populations. Hisp J Behav Sci 1980; 2:199-217
- Szapocznik J, Ścopetta MA, Kurtines W, et al: Theory and measurement of acculturation. Interamerican J Psychol 1978; 12:113-130
- National Center for Health Statistics: Plan and Operations of the Hispanic Health and Nutrition Examination Survey, 1982– 84, Vital and Health Statistics, Series 1, Number 19: DHHS Publication PHS 85-1321. Washington, DC, US Government Printing Office, 1985
- Shapiro S, Skinner EA, Kessler LG, et al: Utilization of health and mental health services: three Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1984; 41:971–978
- 25. Shah BV: SESUDAAN. Standard Errors Program for Computing of Standardized Rates from Sample Survey Data. Research Triangle Park, NC, Research Triangle Institute, 1981
- 26. Regier DA, Goldberg ID, Taube CA: The de facto US mental health services system. Arch Gen Psychiatry 1978; 35:685-693
- Wells KB, Manning WG Jr, Duan N, et al: Cost Sharing and the Demand for Ambulatory Mental Health Services: Publication R-2960-HHS. Santa Monica, Calif, RAND Corp, 1982
- Horgan CM: Specialty and general ambulatory mental health services—comparison of utilization and expenditure. Arch Gen Psychiatry 1985; 42:565–572
- 29. Taube CA, Kessler L, Feuerberg M: Utilization and Expenditures for Ambulatory Mental Health Care During 1980—National Medical Care Utilization and Expenditure Survey Data Report 5: GPO Number 0-421-700/1001. Washington, DC, US Department of Health and Human Services, Health Care Financing Administration, 1984

## A Field Test of Motto's Risk Estimator for Suicide

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The authors undertook a field test of Motto and colleagues' Risk Estimator for Suicide by selecting a subset (N=593) of psychiatric patients with major or chronic affective disorder that corresponded to Motto's sample. They rated each subject on Motto's scale, using standardized data collected at hospital admission. Fourteen patients (2.4%) in their sample and 136 (4.9%) in Motto's sample died by suicide within 2 years. The authors tested the null hypothesis of a uniform suicide risk across all 10 deciles of risk scores by comparing observed and expected frequencies of suicide using the variance test for homogeneity of the binomial distribution. Their findings raise questions about Motto's risk scale but do not definitively invalidate it.

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P sychiatric patients are at much higher risk for death by suicide than the general population. The annual suicide rate is 15–19/100,000 for the adult general population (1), 230/100,000 for those with depression, 270/100,000 for those with alcoholism, and 140/100,000 for those with schizophrenia (2–5). It is estimated that over a period of 15–20 years 10%–15% of all patients with depression, alcoholism, or

schizophrenia die by suicide (2–5). Thus, clinicians are constantly faced with the difficult task of separating the patients at highest risk from the patients at less high risk. Ideally, the clinician will be able to detect which individuals are at highest risk and then discern the time interval of greatest risk with enough certainty to initiate an effective intervention.

The challenge posed by this clinical situation has spawned great interest in the development and validation of standardized clinical instruments for predicting suicidal behavior (6), although no one instrument has been widely adopted. One reason is that most high-risk profiles have been developed by studying suicide attempters, when evidence suggests that those who die by suicide and those who survive suicidal attempts are substantially different populations (7). Another reason is the relative lack of opportunities to cross-validate instruments or replicate findings, because suicide is a statistically rare event.

Motto et al. (6) assessed 2,753 adults hospitalized for a depressive or suicidal state (i.e., suicide had been attempted, threatened, or contemplated) with a standardized clinical interview consisting of 101 psychological and social variables and after a 2-year follow-up found that 136 patients (4.9%) had committed suicide. By repeated partition of their sample, they entered 50 variables showing the most significant univariate relationship with outcome into a series of linear logistic regressions to produce five risk-estimation equations encompassing 44 variables. Using the entire sample, they then performed a logistic regression on the latter 44 variables to produce a final riskestimation equation consisting of 15 variables. Motto and colleagues emphasized that "it remains to field-test the risk assessment instrument to determine its usefulness and characteristics in the clinical setting." We report on a test of Motto's hypothesis that the risk estimator scale can prospectively identify subgroups of patients demonstrating higher or lower rates for completed suicide.

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#### **METHOD**

The NIMH Collaborative Program on the Psychobiology of Depression is being conducted at hospitals associated with five academic centers: Harvard Medical School in Boston, Rush-Presbyterian-St. Luke's Medical Center in Chicago, the University of Iowa in Iowa City, New York State Psychiatric Institute in New York City, and Washington University School of Medicine in St. Louis. The intent and design of the overall study have been described elsewhere (8). Inpatients and outpatients who agreed to undergo diagnostic interviews on admission and follow-up interviews at 6-month intervals for 2 years were recruited for nosologic, familial, and follow-up studies of affective disorder. Patients were seeking psychiatric treatment through the customary referral mechanisms for those institutions. A total of 954 subjects (80% inpatients) were entered into the study. The sample was stratified by diagnosis according to Research Diagnostic Criteria (RDC) (9): 599 patients had unipolar depression, 175 had bipolar type I, 92 had bipolar type II, and 88 had schizoaffective disorder. Patients were also required to be at least 17 years old, Caucasian, and fluent in English and to have an IQ above 70, no evidence of acute or chronic brain syndrome, and knowledge of their biological parents.

By confining our attention to inpatients aged 18–70 years who were admitted during a depressive phase of their illness and by excluding those with nonsuicidal deaths that occurred during the 2-year follow-up, we created a sample of 593 patients who are similar diagnostically to those in the sample studied by Motto and colleagues (6).

Of the 593 patients, 351 (59%) were women; 21 (4%) were 18–19 years old; 184 (31%) were 20–29 years old; 163 (27%) were 30–39 years old; 83 (14%) were 40–49 years old; 81 (14%) were 50–59 years old; 58 (10%) were 60–69 years old; and three (0.5%) were 70 years old. Symptom features for the current episode of affective disorder were assessed shortly after admission by clinical raters using a structured interview (the Schedule for Affective Disorders and Schizophrenia) (SADS) (10) and trained to a high level of interrater reliability (11).

The lifetime course of affective disorder by RDC for the 593-patient sample was bipolar I (major depression and mania) for 61 patients (10%), bipolar II (major depression and hypomania but never mania) for 78 patients (13%), recurrent unipolar (two or more major depressions, never mania or hypomania) for 271 patients (46%), and currently schizoaffective manic or depressed for 13 patients (2%); the remainder were in a first episode of major affective disorder or in a chronic (2 years or more) intermittent episode of depressive disorder. At intake, 115 patients (19%) met criteria for psychotic subtype (delusions or hallucinations) major depression, 95 (16%) evidenced no suicidal ideation in the current episode, 251 (42%) evidenced mild to moderate suicidal ideation, and 249

(41%) evidenced severe suicidal ideation. Of the 214 patients (36% of 593) who had made a suicide attempt, 53 (25%) made a genuinely life-threatening attempt (e.g., cut throat, respiratory arrest, coma), and another 111 (52%) made a medically serious attempt (e.g., ingestion of 10 aspirin with gastric upset; ingestion of 10 Seconal with brief unconsciousness).

To select the appropriate variables for analysis, we identified all sociodemographic, clinical, and psychosocial variables from the SADS and other structured assessment instruments that might correspond to the 15 items of Motto's Risk Estimator for Suicide (6). We then submitted this pool of potentially appropriate variables (i.e., the rating or self-report items and their scoring conventions) to Motto for review. Motto then selected a subset that corresponded best to the items of the Risk Estimator for Suicide. The match was reasonably good for 14 items. For item 15 (interviewer's negative or positive reaction to the person), behavioral ratings of self-pity and dependency were used to estimate specific aspects of that reaction. Thus, a Motto Risk Estimator for Suicide score was calculated for each patient in our sample on the basis of an initial assessment at hospital admission.

At each 6-month follow-up point, the status of at least 96% of the sample could be determined. Determination of a "death by suicide" outcome was based on information from family members, clinicians familiar with the patient, and coroners' reports. Treatment was uncontrolled, varying from center to center and patient to patient, but was systematically recorded during the follow-up.

#### **RESULTS**

Motto and colleagues observed that 4.9% of their patient sample died by suicide within 2 years of hospital discharge (6), a rate higher than the 1%–2% per year for depressed patients estimated by several studies (7, 12). By contrast, only 14 of our 593 patients (2.4%) died by suicide within 2 years of study admission, a rate at the low end of the expected range of 2%–4% for 2 years of follow-up. The large disparity in suicide rates (4.9% versus 2.4%) may reflect differences in the clinical management of patients. Motto and colleagues collected patients from seven community mental health centers, a municipal general hospital, and a university-based psychiatric hospital. All of our patients were admitted to major university medical centers

The number of patients falling into each of the 10 risk score decile ranges (as defined by Motto and colleagues) is detailed in table 1. Risk scores for the patient sample were for the most part evenly distributed among the 10 decile ranges, although we observed an excess of patients in the lowest risk decile and a slight deficit of patients in the two highest risk deciles

Table 1 also details the number of patients who died

TABLE 1. Estimated and Observed Incidence of Suicide for 593 Depressed Inpatients During 2-Year Follow-Up

Decile	of S	Distribution of Subjects (N=593)		erved dence uicide =14)	Frequ Su	Expected Frequency of Suicide (N=14)a		
of Risk	N	%	N	%	N	%		
1	92	15.5	2	2.2	2.2	2.36		
2	59	9.9	1	1.7	1.4	2.36		
3	49	8.2	2	4.1	1.2	2.36		
4	70	11.8	0	0.0	1.6	2.36		
5	49	8.2	1	2.0	1.2	2.36		
6	58	9.7	3	5.2	1.4	2.36		
7	61	10.2	2	3.3	1.4	2.36		
8	61	10.2	1	1.6	1.4	2.36		
9	48	8.0	2	4.2	1.1	2.36		
10	46	7.7	0	0.0	1.1	2.36		

<sup>&</sup>lt;sup>a</sup>Equal risk hypothesis.

by suicide in each of the risk deciles. If Motto's hypothesis were true, we would expect that the frequency of suicide would increase as the score decile increased. This did not appear to be the case. Six of 14 patients who died by suicide (43%) were classified in the lowest five risk deciles; only three (21%) were classified in the highest three risk deciles.

The observed pattern of suicides can be tested statistically against the null hypothesis of an equal distribution of suicides across all 10 risk deciles (i.e., no pattern) by means of a chi-square test (the variance test for homogeneity of the binomial distribution) (13). The null hypothesis assumes a binomial distribution of risk with uniform probability over all risk deciles (i.e., the probability of suicide for each risk decile= 14/593=2.36%). A comparison between the observed and expected number of suicides by decile yielded no evidence to reject the null hypothesis of a uniform distribution of suicides ( $\chi^2=6.46$ , df=9).

One might ask whether our sample size is large enough for a useful test of Motto's hypothesis. We tested the distribution of 14 suicides over 10 risk decile groups; Motto examined the distribution of 136 suicides over the same 10 groups. It is possible that the risk of a type II error (i.e., failing to reject the null hypothesis, which is in fact false) is simply too high for the results of our smaller study to be taken as definitive. Therefore, we performed a power analysis of the chi-square statistic (14), assuming that Motto's expected distribution of suicides is the true population distribution. Setting the type I error rate (alpha) at .05, we obtained a power coefficient of .67 for our sample of 14 suicides. To achieve a power level of .90, the calculation indicates we would require a sample of 24 suicides.

The results of this power analysis suggest that if Motto's hypothesis were true for our sample, we would succeed in rejecting the null hypothesis two-thirds of the time. This represents a substantial degree of power achieved with a sample of substantial size, but the risk of type II error is too high for our results

to be interpreted as definitive. The results also suggest that if we had attained a sample size that included 24 suicides, we could successfully reject the null hypothesis under the same conditions 90% of the time. Twenty-four suicides in a sample of 593 subjects represents a suicide rate of 4.0%, a rate at the high end of the expected 2%-4% range (7, 12) but lower than the higher rate (4.9%) observed in Motto's sample. Since we observed a suicide rate of 2.4% in our sample, we calculate that we would have to increase our sample size to 1,000 patients to encompass the 24 suicides necessary to achieve a power level of .90.

#### DISCUSSION

Although suicide occurs relatively frequently in a large sample of depressed patients, it still has a statistically low base rate and therefore may be statistically unpredictable on an individual basis, particularly when the data base is limited to a cross-sectional assessment (15). Suicide may also be a behavioral outcome reached through so many different pathways that no constant set of clinical features can serve as an accurate prediction equation.

Our sample exhibited a distinctly lower suicide rate over 2 years of follow-up than the one reported for Motto's sample. It is unlikely that this lower rate is an underestimate due to faulty verification procedures or incomplete follow-up, since only 4% of the patients could not be located at the 2-year follow-up. It is also unlikely that the population our sample represents is less severely depressed or less functionally impaired than Motto's population, since our university medical center settings engage in a great deal of tertiary care for patients referred from community hospitals and mental health centers. It is possible that the quality or intensity of clinical care available to the patients at these university medical centers during and after hospitalization (particularly follow-up care) minimizes the incidence of suicide, but this hypothesis is impossible to ascertain in the absence of a control group.

A question remains about the diagnostic comparability of our sample and that studied by Motto and colleagues, despite our efforts to match them. Motto did not employ a standardized clinical interview and did not assess rater reliability, so it is impossible to compare the two samples by diagnosis. In particular, it is impossible to gauge the proportion of Motto's sample who did not evidence affective disorder or the proportion with concomitant affective and nonaffective (e.g., alcoholism) disorders. Major differences between the two samples on either count might explain why Motto's prediction equation does not generalize to our sample. Other factors that might contribute to the discrepant results include the fact that the rating items we employed were not identical to those employed by Motto and the sample sizes and racial constitutions of the two samples (23% of Motto's sample was nonwhite) were different.

Although our findings raise questions about Motto's Risk Estimator for Suicide, they do not definitively invalidate the scale. If investigators use the scale, they should do so with caution until further evaluation can settle the questions. Our findings also highlight the likelihood that suicide scales derived by multivariate analysis of a large number of clinical, psychosocial, and demographic variables may tend to be arbitrary and sample specific. Our impression is that empirically-derived scales based on a single cross-sectional assessment are always difficult to validate. Repeated assessments over time on a broad array of clinical features may be necessary to develop an adequate and replicable prediction system. We propose that serial assessments which pay attention to the vicissitudes of clinical symptoms, changing life stress, and long-standing character structure in concert (16) would provide a better method of estimating suicide risk.

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- Centers for Disease Control: Suicide Surveillance, 1970–1980. Atlanta, US Department of Health and Human Services, April 1985
- 2. Miles CP: Conditions predisposing to suicide. J Nerv Ment Dis 1977; 164:231–246
- Bleuler M: The Schizophrenic Disorders: Long-Term and Family Studies. New Haven, Yale University Press, 1978
- Tsuang MT: Suicide in schizophrenics, manics, depressives and surgical controls. Arch Gen Psychiatry 1978; 35:153–154
- Berglund M: Suicide in alcoholism. Arch Gen Psychiatry 1984; 41:888–891
- Motto JA, Heilbron DC, Juster RP: Development of a clinic instrument to estimate suicide risk. Am J Psychiatry 1985; 142: 680-686
- Stengel E: A survey of follow-up examinations of attempted suicide, in Suicide and Attempted Suicide. Edited by Waldenstrom J, Larson T, Ljungstedt N. Stockholm, Nordiska Bokhandelns Forlag, 1972, p 251
- 8. Katz MM, Klerman GL: Introduction: overview of the clinical studies program. Am J Psychiatry 1979; 136:49-51
- Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773–782.
- Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
- Keller M, Lavori P, Andreasen N, et al: Test-retest reliability of assessing psychiatrically ill patients in a multi-center design. J Psychiatr Res 1981; 16:213–227
- Guze SB, Robins E: Suicide and primary affective disorders. Br J Psychiatry 1970; 117:437

  –448
- Snedecor GW, Cochran WG: Statistical Methods, 6th ed. Ames, Iowa State University Press, 1967
- Cohen J: Statistical Power Analysis for the Behavioral Sciences, revised ed. New York, Academic Press, 1977, p 216
- Murphy GE: On suicide prediction and prevention. Arch Gen Psychiatry 1983; 40:343-344
- Smith K: Suicide and assessment: an ego vulnerabilities approach. Bull Menninger Clin 1985; 49:489–499

## The Initial Contract in the Treatment of Borderline Patients

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The initial treatment contract with a borderline patient recognizes the patient's potential for destructiveness and builds in safeguards. The therapist's effort to protect the treatment mobilizes the patient's primitive defenses. The therapist must be prepared to respond to resistance to the contract by clarification, confrontation, and occasionally interpretation. Although countertransference reactions evoked by the patient's use of primitive defenses complicate the therapist's task of defining the necessary treatment frame, the therapist's recognition of countertransference responses can enable him to establish and enforce an appropriate contract.

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he treatment of borderline patients is complicated ■ by the instability that characterizes the borderline personality structure. These patients are subject to storms of affect, impulsive and potentially self-damaging behavior, tumultuous interpersonal relationships, and transient regressive states. In addition, their interpersonal defensive patterns evoke powerful countertransference reactions in the therapist. A number of treatment approaches have been recommended, from supportive to classically psychoanalytic (1-4), to be carried out in settings ranging from unstructured outpatient practice to highly regimented inpatient facilities (5). While there continues to be an unfortunate dearth of empirical studies on treatment for borderline patients (6-9), clinicians seeking characterological change in these patients often employ psychodynamic psychotherapy. This article proposes the use of a treatment contract to enhance the possibility of keeping more in treatment.

For a few borderline patients, the standard introductory remarks that are given to all patients who begin dynamic psychotherapy are sufficient (10, 11). These remarks typically include a brief explanation of how psychotherapy will work to help the patient, a recom-

mendation about frequency of sessions, instructions to the patient about his task in the session (e.g., "Try to speak freely and openly about whatever is on your mind without making decisions about what is or is not important to say"), negotiation of the fee and regular appointment times, and specification of the therapist's expectations about payment of the fee, handling of missed appointments, and vacation arrangements. This introduction defines the roles of both patient and therapist and establishes a framework within which the treatment can be practically conducted.

Patients who need more than this standard introduction make clear, either through the history they give or their behavior in the diagnostic interview, that their ability to form an alliance is severely restricted (12) and they are prone to act out. Typical indicators in their history include evidence of sabotage of prior treatment opportunities, manipulative suicide attempts, life-threatening symptoms, anorexia nervosa with severe weight loss, or antisocial behavior. Behaviors during the consultation may also signal the need for negotiation of a contract: the patient's proposal of precarious means to finance the treatment; his squandering of time in the first meeting by arriving very late, insisting on leaving very early, or remaining silent for much of the session; or his arrival at the consultation under the influence of drugs all suggest the possible need for a carefully designed initial contract. The usual therapeutic environment is not sufficient to contain such patients, and unless the therapist provides specific structures, these patients pose a serious danger to themselves, the therapist, or the treatment.

This paper examines the process of establishing a treatment contract. The term "contract," borrowed from the world of business and the law, is particularly apt because it emphasizes the need to begin with a mutual agreement that is explicit, that specifies the responsibilities of both parties, and that is arrived at through negotiation, not fiat. If properly conceived, the initial contract protects the early treatment until a working relationship has been established between patient and therapist.

#### FORMULATING THE CONTRACT

The therapist must address the danger to the treatment before considering any other subject except an imminent danger to the patient's or other persons'

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lives. The issue is not how the treatment should be conducted but whether the treatment can take place at all, and, if so, under what conditions. The therapist should proceed in the following sequence: 1) Point out how the treatment situation is threatened by the patient's pathology, specifying the nature of the threat; 2) indicate the realistic limitations in the therapist's ability to deal with the situation alone and the need for the patient's help, thus eliciting whatever interest and support the patient has in collaborating with the therapist to make treatment possible; and 3) detail an initial treatment contract that offers protection to the treatment effort.

Ideally, this plan should have explicit guidelines so as to avoid debates over the subtleties of what constitutes a threat to treatment. For example, if the patient has a history of anorexia, the initial contract includes a nonnegotiable baseline weight that the patient must maintain for the treatment to continue and a delineation of the therapist's response if the patient were to fall below that weight.

The therapist introduces the minimum structure necessary to safeguard the frame. Before introducing any limit, he clarifies what the patient is saying or doing that is causing him to introduce the particular boundary. This sets the stage for the later analysis of the guideline introduced. For example, "Since you are telling me that if you don't return to school you will alienate your family and they will withdraw support for your treatment, you are indirectly insisting that I tell you to go back to school. Why you can't tell that to yourself but rather insist that I do it for you is unclear at this moment. It's something we will have to understand, but for now, it's clear you have to return to school if you are to be in treatment."

The need for the structure should be analyzed as soon as sufficient groundwork has been established. This allows the patient to understand his motivation for projecting responsibility onto the therapist, so that he can eventually assume the limit-setting responsibility for himself. For example, "Last month I had to advise you to go back to school and get your degree because at the time it was as if you had deposited in me your own concern for yourself, while at the same time testing me as to whether I would allow you to go down the drain. Now that you're back in school, I think it's important that we discuss all your feelings about going back to school, including the negative ones. And I think we should also discuss what it means to you that I should have been put into a position of pushing you into going back to school."

It is important that the patient be instructed that the therapist has a range of responses which he can utilize when the patient violates or threatens to violate the treatment contract. These reactions run the gamut from simple confrontation and interpretation within the interview situation to suspending a particular session or enlisting the aid of others, to finally terminating the treatment. The therapist should exercise the least restrictive measure possible.

#### PATIENT RESISTANCES TO THE CONTRACT

Borderline patients oscillate between the expectation that little will be required of them while much will be given to them (those with strong narcissistic features) and profound feelings of inadequacy and lack of a sense of entitlement (those with strong masochistic trends) or else a belief that they will be treated in a malevolent fashion, necessitating their protecting themselves from others (those with marked paranoid tendencies).

Raising the issue of a contract threatens the patient's precarious sense of self. He may feel his grandiosity challenged and his worthlessness confirmed. As Horowitz (13) points out, "to protect against the chaotic and despairing experience of entry into states of bad self images, the borderline person attempts to use any other way of structuring the world that can be stabilized by even marginal adherence to reality" (p. 552). To protect his world, the patient resorts to his characteristic repertoire of defensive operations, typically omnipotent control, projective identification, devaluation, splitting, and primitive denial. Efforts at setting the contract inevitably include confronting the patient's use of these defenses. The following example illustrates such a sequence.

The patient sought treatment with his fourth therapist, explaining that his three previous doctors had "quit on him" because of his episodic attendance at sessions. When his new doctor informed him that he would be expected to come to his appointments regularly, the patient responded indignantly. "How can you expect me to change my behavior right away? Isn't this why I'm coming to you in the first place?" The therapist acknowledged his appreciation of the patient's dilemma and then asked, "Can you understand that if, in fact, you are unable to come to sessions, I am unable to help you?" The patient said he intellectually understood but insisted that, "I just know you could find some way to bend your rules for me. Otherwise, you're just like all my other doctors who were more interested in keeping to their own schedules than in understanding me."

When the therapist confronted the patient with his grandiose wish and suggested a variety of possible structures, including hospitalization, to facilitate the patient's keeping appointments, he responded, "It's true I can't think of a way we can work together if I don't come to see you, and I know that coming into the hospital and several other things you suggested might well work. But, if I did that, I feel I'd be giving up. Besides, I keep thinking that you're holding out on me, and if I keep insisting, you'll eventually reveal some special way to work with me on my schedule."

This example illustrates several characteristic dilemmas the therapist faces in his efforts to establish the contract. Through the use of splitting, the patient's intellectual comprehension of the impossibility of his demand does not influence the rest of his thinking. By attributing excessive demandingness and rigidity to the therapist, the patient defends against his own voracious wishes that, through projective identification, are now perceived as residing within the therapist. The

patient's unconscious recognition that he must preserve his fantasy of omnipotent control at all costs, even if it means sabotaging the treatment, is illustrated by his reference to feeling he would be "giving up" by going into the hospital. Finally, the patient alternatively views himself and the therapist as grandiose and devalued. The patient perceives the therapist as cruel, withholding his "special way" of conducting therapy in a manner that would allow the patient not to have to attend; at the same time, the patient sees himself as able to magically force the secret out of the therapist. An appropriate therapist interpretation would be, "Although you experience me as making outrageous demands on you, in fact you are the one who is demanding that I do the impossible. You are asking me to treat you even if you don't show up."

# COUNTERTRANSFERENCE AS A COMPLICATING FACTOR

The therapist's reactions may inhibit his ability to establish an appropriate contract. The therapist may react to the patient or to the process of having to set limits. These factors are intimately connected. The therapist's attitude toward setting limits provokes the patient's primitive responses, and the patient's rage, idealization, devaluation, and efforts to control the treatment confound the therapist's ability to set limits.

What is there about borderline patients that evokes such strong countertransference in one or two sessions? Borderline patients are extremely vulnerable to dyadic relationships (14), often have an eerie empathic understanding of the vulnerability of others (15), and can rapidly mobilize primitive transferences that are chaotic, demanding, ambiguous, and oscillating. All these factors contribute to making the initial sessions confusing for patient and therapist. The therapist's agenda in the initial sessions is to explore in what way the two participants might work together, while the patient focuses on his predetermined ideas about the personality, ambitions, and prejudices of the therapist.

It is no wonder that the therapist quickly develops powerful reactions to the patient. The therapist's subsequent behavior derives not only from what the patient mobilizes in him but also from his own efforts to bring a premature, pseudostabilization to the chaos. That is, rather than to stay with and try to sort out the multiple projections the patient is bombarding him with, the therapist may unconsciously select out one response so that he does not have to deal with the contradictory reactions he is experiencing. Before the therapist can develop even a rudimentary understanding of who the patient is or what he might want, the therapist finds himself assigned a variety of conflicting, challenging, and changing roles: He is treated by the patient as the good figure, the bad figure, the one who must make things better, the agent of the patient's downfall, indifferent, overinvolved, and the last hope. Indeed, the therapist's countertransference reactions frequently mirror the role he has selected from the many the patient has assigned him.

Common therapist responses include a wish to rescue the patient, paranoid concerns about the patient's attacking him, a search for narcissistic gratification in the interaction, and/or an unwarranted sense of hopelessness. The following vignettes illustrate how these reactions interfere with the therapist's ability to establish an effective treatment plan.

In assessing a patient who has a history of multiple suicide attempts and who reports current impulsive suicidal feelings, the therapist does not consider hospitalization as an option but immediately feels a strong wish to make himself continuously available to the patient to protect her from her impulses. He believes that were she to go into the hospital, the staff would overlook the seriousness of her illness and not be as attentive to her as he would.

An abusive and demanding patient refuses to agree to any of the structuring conditions prescribed by the therapist as essential preconditions for treatment. The therapist, although recognizing the need for limits, is afraid to refuse to treat the patient, imagining that if he did so the patient's family would sue him for malpractice.

A well-known rock star with a history of drug dealing, stealing, and lying is referred to the therapist by a well-known colleague. Feeling intrigued by the patient's glamorous lifestyle and honored by the colleague's referral, the therapist agrees to undertake dynamic psychotherapy without carefully considering its contraindication in view of the patient's severe antisocial behavior.

A patient reports several abortive experiences in psychotherapy with therapists whom she denigrates, and is devaluing and condescending to the therapist during the initial evaluation. Without inquiring about the nature of her prior therapy experiences, the backgrounds of her previous therapists, or her understanding of what took place, especially in relation to her own contribution, the interviewer concludes that the patient is not amenable to psychotherapy.

One of the most important functions of the initial contract is to set limits. A therapist who has not resolved his own issues about omnipotence, dependency, or sadism will have difficulty with this aspect of the contract. Omnipotent countertransference (16) prevents the therapist from recognizing that he requires something from the patient. Instead he feels that he can and should cure the patient all by himself. Such a therapist, faced with a patient with a history of having been evasive and withholding of crucial information in her previous treatment, would have difficulty saying, "I insist upon your being open and honest with me if I am to help you." To the extent the therapist is entangled in his own dependency struggles, he may wish to tell the patient, "If you want to kill yourself, don't call me," when, in fact, he needs to tell her, "If you feel the desire to kill yourself, you must agree to call me." The therapist struggling with his own sadistic impulses may attempt to protect himself by defensively adopting a permissive attitude toward

his patients. Such a therapist will have difficulty distinguishing appropriate limit setting from hostility directed toward the patient. He would have difficulty saying, "If you don't stop getting pills from other doctors, I will have to terminate our work."

#### WHAT IS ACCOMPLISHED

While the establishment of an appropriate initial contract provides the structure to make treatment possible, it also challenges distorted representations of the patient-therapist interaction. To the extent that the therapist demonstrates that he is able to protect himself and the treatment, he communicates to the patient that he is separate, beyond the patient's omnipotent control (17), and thus is a potential source of help (18). This allows the patient to perceive the therapist as capable of containing his projections rather than becoming them. Conversely, to the extent that the patient is able to control or destroy the therapist (or his activities), he becomes what the patient makes of him, is perceived as an extension of the patient, and is rendered less effective.

The contract also establishes the fact that the patient bears responsibility for his treatment to whatever degree he is capable and that psychotherapy is work carried out jointly, each participant having specific responsibilities. The therapist who fails to make clear to the patient that psychotherapy is a collaborative process colludes with the patient's grandiosity (i.e., "I can do anything I want with no bad consequences"), devaluation (i.e., "I need do nothing because the treatment is worthless anyway"), or demand for an omnipotent therapist (i.e., "All I have to do is show up and you will cure me").

The contract not only challenges the patient's sense of specialness and desire to avoid responsibility but also addresses the health-seeking aspect of the patient that wishes to join with the therapist. By the same token, the therapist defines himself as having rights as well as responsibilities. In this way, he provides the patient with a figure for identification who, over time, can aid the patient in forming a more realistic sense of his own entitlement.

Finally, in defining these contractual relationships at the outset, the therapist provides a framework against which he may later explore treatment-damaging behaviors in the context of the transference. For example, "Before, when we agreed to work together, we discussed at length your temptation to alienate your parents from you so that they would stop paying your treatment bills, and by your actions, you would destroy the treatment. Therefore, I find your current abuse of your father to be a way of getting at me."

#### **CONCLUSIONS**

A treatment contract is valuable for stabilizing the initial phase of treatment and providing a frame of reference for the ongoing examination of threats to the continuity of the treatment. Efforts to establish the contract elicit the patient's characteristic defenses, which can evoke countertransferences that may sidetrack the therapist from completing the task.

- Zetzel ER: A developmental approach to the borderline patient. Am J Psychiatry 1971; 128:867–871
- Grinker R, Werble B: The Borderline Patient. New York, Jason Aronson, 1977
- Kernberg O: The treatment of patients with borderline personality organization. Int J Psychoanal 1968; 49:600–619
- Boyer L: Analytic experiences in work with regressed patients, in Technical Factors in the Treatment of the Severely Disturbed Patient. Edited by Giovacchini P, Boyer L. New York, Jason Aronson, 1982
- Koenigsberg HW: Indications for hospitalization in the treatment of borderline patients. Psychiatr Q 1984; 56:247–258
- Kernberg O, Burstein E, Coyne L, et al: Final report of the Menninger Foundation's psychotherapy research project: psychotherapy and psychoanalysis. Bull Menninger Clin 1972; 34: 1-2
- Stone M: Psychotherapy with schizotypal borderline patients. J Am Acad Psychoanal 1983; 11:87–111
- Waldinger R, Gunderson J: Completed psychotherapies with borderline patients. Am J Psychotherapy 1984; 38:190–202
- Wallerstein RS: Forty-Two Lives in Treatment. The Report of the Psychotherapy Research Project of the Menninger Foundation, 1954–1982. New York, Guilford Press, 1986
- DeWald PA: Psychotherapy: A Dynamic Approach, 2nd ed. New York, Basic Books, 1969
- 11. Gill MM: Analysis of Transference: Theory and Technique, vol 1. New York, International Universities Press, 1981
- Adler G: The myth of the alliance with borderline patients. Am J Psychiatry 1979; 136:642-645
- Horowitz MJ: Cognitive and interactive aspects of splitting. Am J Psychiatry 1977; 134:549–553
- Adler G: Valuing and devaluing in the psychotherapeutic process. Arch Gen Psychiatry 1970; 22:454

  461
- 15. Krohn A: Borderline "empathy" and differentiation of object representations: a contribution to the psychology of object relations. Int J Psychoanal Psychother 1974; 3:142–165
- Greenacre P: Problems of overidealization of the analyst and the analysis. Psychoanal Study Child 1966; 21:143–212
- Dorpat TL: Introjection and the idealizing transference. Int J Psychoanal 1979; 7:26-51
- 18. Winnicott DW: The use of an object. Int J Psychoanalysis 1969; 50:711-776

# Depression, Depressive Symptoms, and Depressed Mood Among a Community Sample of Adolescents

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Using a structured interview, the authors found that the prevalence of major depression and dysthymic disorder was 4.7% and 3.3%, respectively, in a community sample of 150 adolescents. All of the adolescents who met the criteria for major depression and dysthymic disorder had other psychiatric disorders as well; anxiety was the most frequent accompanying DSM-III diagnosis. (Am J Psychiatry 1987; 144:931-934)

he latest edition of the Comprehensive Textbook of Psychiatry acknowledges a lack of empirical data on affective disorders in adolescents in nonclinic populations (1), and several researchers have expressed concern over this issue (2–4). Prevalence estimates of affective disorders in adults have been previously reported by Weissman and Myers (5) and more recently by Myers et al. in a multicenter, NIMHsupported study; Myers et al. reported a 6-month prevalence rate ranging from 4.6% to 6.5% for all affective disorders in adults (6). In a study of a preadolescent group, Kashani et al. reported a prevalence of 1.8% for major depression (7). Thus, data are available for other age groups; however, extrapolation of these data from one age group to another is clearly untenable. For instance, in Rutter et al.'s Isle of Wight study, the 9- and 10-year-old children, re-examined 4 years later, demonstrated a threefold increase in the depression rate from preadolescence to adolescence (8). Rutter et al. also reported that more than 40% of the adolescents expressed feelings of depression and misery during the interview. Interestingly, self-rating revealed feelings of depression much more frequently in the adolescents than in their parents, again under-

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scoring the specificity of affective symptoms with regard to age (8).

Although empirical data for estimating the prevalence of depressive disorder have been lacking, data on the frequency of depressive symptoms exist. For instance, Kandel and Davies administered a six-item self-report inventory to adolescents (13-19 years) and their parents, with female adolescents reporting significantly more depressive symptoms than their male counterparts. They also found that the adolescents reported more symptoms than their parents, and that among the parents, mothers had more depressive symptoms than the fathers (9). Kaplan et al. have also reported on the prevalence of depressive symptoms in adolescents, using the Beck Depression Inventory (10). Cognizant of the limitations of their study, Kaplan et al. stated that "validating the prevalence of major depressive disorder in adolescents with a structured psychiatric interview in a general adolescent population merits further investigation."

The purpose of the present study is to fill in some of these gaps, namely 1) to determine the existence of depressive disorder in a nonclinic sample, and given its existence, to determine prevalence rates and identify subtypes; 2) to study adolescents who manifest depressive symptoms but who do not meet the full criteria for depressive disorder, in order to explore the entire spectrum of depression (11), ranging from the mildest forms to full-blown syndromal depression as defined by DSM-III; and 3) to specify the coexistence of other psychiatric disorders with depression.

#### **METHOD**

We studied 150 subjects age 14, 15, and 16 years in the ninth, 10th, and 11th grades, representing 7% of all adolescents attending public schools in Columbia, Mo. They were systematically solicited from an initial pool of 1,700 to form a total group comprising 50 of each age and 75 of each sex. In order to keep the homogeneity of the group, only those 14, 15, and 16 years old who did not change age during the data collection period (5 months) were selected. The majority (about 95%) were Caucasian, and the rest were

black or Oriental. Their socioeconomic status, based on Hollingshead and Redlich's two-factor social class index, was as follows: class I, 10.7%; class II, 31.3%; class III, 29.3%; class IV, 27.3%; and class V, 1.4%. Subject participation was solicited by telephone, and during the phone interview the study was introduced. Every effort was made to keep the acceptance rate high. This included conducting an interview at the homes of participants and offering a \$20 fee as compensation for their time. These efforts led to an overall acceptance rate of 72.4%. During the telephone interview, socioeconomic status data were all that we could obtain from the families who refused to participate. The mean socioeconomic status for the refusal subjects was 2.9 and for the 150 participants, 2.7 (Mann-Whitney U test, p=n.s.).

Subjects who agreed to participate were scheduled for a home interview. Both parents (if available) and the adolescents were asked to sign a consent form as required by the institutional review board of the University of Missouri—Columbia. The adolescent and the parents were reassured about the confidentiality of the data obtained. During the home visit, the adolescent was interviewed with the Diagnostic Interview for Children and Adolescents and the parents with the Diagnostic Interview for Children and Adolescents: Parent Version (12, 13). Since these instruments do not include dysthymic disorder, we modified them, adding questions from DSM-III criteria for dysthymic disorder (Z. Welner, personal communication, 1985).

Interviews were conducted by three clinicians with M.A. degrees who were Ph.D. candidates in psychology. Interrater agreement of at least 95% was obtained, and ongoing supervision of the recording of subjects' responses was continued throughout the study. For the first 20 subjects, each interviewer was observed by one of the other two, who also recorded the subjects' responses on the interview measure and parents' responses on the parent version. Retraining exercises were also conducted after every 30–50 interviews in order to minimize rater drift (14).

At the end of each interview, the interviewer made a clinical judgment as to whether any diagnosis based on DSM-III existed and, if so, whether treatment was necessary. A "case" was defined as an individual who met the criteria for any DSM-III diagnosis and who, in the clinician's judgment, was dysfunctional and needed treatment. A child psychiatrist (J.H.K.) reviewed the interview data from the adolescents and the parents; his agreement with the interviewers on the diagnosis and need for treatment was required. Another child psychiatrist (G.A.C.) independently reviewed the information from the adolescents and their parents, and full agreement between the two child psychiatrists (J.H.K. and G.A.C.) also was required for diagnosing depression cases in this sample. Therefore, any subject who had depressive symptoms but for whatever reason was not diagnosed as depressed by any of the three sources (the clinician or either of the two child psychiatrists) was included in another group labeled "with depressive symptomatology." This group included subjects whose interviews indicated the presence of symptoms requisite for major depression or dysthymic disorder but with 1) insufficient duration of symptoms, 2) a clinician's judgment that treatment was not necessary, or 3) the adolescent's statements during the interview that his or her depression did not interfere with his or her work (i.e., depressive symptoms resulted in minimal dysfunction).

#### RESULTS

Of the 150 adolescents, 7 (4.7%) were found to have major depression. However, all of these subjects met the criteria for dysthymic disorder as well. Therefore, major depression and dysthymia coexisted in these individuals (double depression) (15). Five other adolescents (3.3%) were also found to meet the criteria for dysthymic disorder. Hence, 12 adolescents (two boys and 10 girls), or 8% of the total sample, met the criteria for some type of depressive disorder on the basis of *DSM-III*.

In addition, 33 other adolescents (11 boys and 22 girls) reported depressive symptoms but did not meet the requirement for caseness; namely, their depressive symptoms did not result in their being dysfunctional, nor were they rated as needing treatment. They did, however, meet the symptom counts for major depression or dysthymic disorder. In this study, this group will be referred to as "with depressive symptoms."

Finally, 28 adolescents reported dysphoric mood for either 2 weeks (N=20) or 1 year (N=8). The remaining 77 adolescents did not report any type of dysphoric mood.

A comparison of the 12 depressed individuals with the 33 who had depressive symptoms failed to show significant differences in sociodemographic variables such as age, sex, race, socioeconomic status, parents' marital status, and so forth. However, the two groups differed in several ways. For instance, every individual in the depressed group had another *DSM-III* diagnosis, whereas only 61% of the group with depressive symptoms had an accompanying *DSM-III* diagnosis. In addition, the diagnosis of anxiety disorder was significantly more frequent in the depressed group than in the group with depressive symptoms (nine of 12 [75%] versus seven of 33 [21%]; Fisher's exact test, p<.002).

With regard to the coexistence of a DSM-III diagnosis in the four groups of adolescents, all of the 12 depressed adolescents had additional diagnoses: 75% (N=9) had anxiety disorder, 50% (N=6) had oppositional disorder, 33% (N=4) had conduct disorder, 25% (N=3) had alcohol abuse, and 25% (N=3) had drug abuse; there were also single cases of mania, attention deficit disorder, and enuresis. In the group with depressive symptoms (N=33), 61% had a DSM-III diagnosis; the three most common were anxiety

disorder (21%, N=7), oppositional disorder (18%, N=6), and drug abuse (15%, N=5). Of the 28 individuals with dysphoric mood, 36% had a DSM-III diagnosis; the two most common were anxiety disorder (21%, N=6) and oppositional disorder (18%, N=5). Finally, 26% of the remaining 77 subjects were found to have a DSM-III diagnosis (i.e., oppositional disorder, 10%, N=8; conduct disorder, 9%, N=7; and anxiety disorder, 5%, N=4). A comparison of the above four groups of adolescents (N=12, 33, 28, and 77) for additional diagnoses considering ordered categories indicated the existence of a significant trend (100% versus 61% versus 36% versus 26%;  $\chi^2$ = 29.92, df=3, p<.005) (16, 17).

#### DISCUSSION

Data regarding epidemiology of psychiatric disorders among adolescents remain scanty, despite burgeoning interest in adolescent mental health (4). The present study provides information on the prevalence of adolescent depression in a community sample of adolescents between the ages of 14 and 16, with a reported prevalence of 4.7% for major depression and 3.3% for dysthymic disorder. The reported prevalence among adolescents in this study is higher than that previously reported for preschoolers (18) and more than twice the reported prevalence in school-age children (7). This is in agreement with Rutter, who found that depression increased threefold from preadolescence to adolescence (19). In addition, Rutter et al. (8) reported that nearly half of adolescents from a general population sample admitted during direct interviews to appreciable misery or depression, a finding similar to our own (N=73, 48%). However, the prevalence of depressive disorders in this study is comparable to that found in Myers et al.'s adult study, documenting prevalence ranges of 2.2%-3.5% and 2.1%-3.8% for major depression and dysthymic disorder, respectively, among a group of 18-24-year-olds (6).

It is interesting to note that all the adolescents who met criteria for depression had other psychiatric disorders as well. This may be a result of our selection process, which required evidence of impairment of functioning as well as the need for treatment for each case. In each of the three groups of adolescents (those with depression, depressive symptoms, or dysphoric mood), anxiety disorder was the most frequent accompanying DSM-III diagnosis.

Although *DSM-III* describes associated features of depression in boys (e.g., grouchiness, negativism, antisocial behaviors, alcohol and drug abuse), corresponding associated features in girls are not addressed. Since the present study found more girls both in the depressed group and in the group with depressive symptoms and because anxiety was found to be the most common disorder and affect associated with depression, this study provides information that is lacking in *DSM-III*.

In the present study, additional *DSM-III* disorders correlated positively with increasing severity of depression. The reason for this increase in accompanying *DSM-III* disorders is unknown. However, a recent study reported by Boyd et al. (20) found that disorders which are related to each other according to *DSM-III* were more strongly associated than unrelated conditions. In general, the tendency toward a co-occurrence was such that the presence of any psychiatric disorder increased the odds of having any other *DSM-III* disorder.

Follow-up of adolescents with depressive symptoms is not only of interest but also necessary. Akiskal et al. (21) reported that an atypical case of neurotic depression, which they consider the most frequent type in adolescents, is a precursor to a later clear-cut affective disorder. Further study will be necessary to determine how many teenagers with depressive symptoms not currently impairing their function will later suffer more pervasively from their symptoms.

- Puig-Antich J: Affective disorders, in Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Edited by Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1985
- Carlson GA, Strober M: Affective disorders in adolescence, in Affective Disorders in Childhood and Adolescence: An Update. Edited by Cantwell DP, Carlson GA. New York, Spectrum Publications, 1983
- 3. Ryan ND, Puig-Antich J: Affective illness in adolescence, in Psychiatry Update: American Psychiatric Association Annual Review, vol 5. Edited by Frances AJ, Hales RE. Washington, DC, American Psychiatric Press, 1986
- Garrison CA, Schoenbach VJ, Kaplan BH: Depressive symptoms in early adolescence, in Depression in Multidisciplinary Perspective. Edited by Dean A. New York, Brunner/Mazel, 1985
- 5. Weissman WM, Myers JK: Affective disorders in a US urban community. Arch Gen Psychiatry 1978; 35:1304-1311
- 6. Myers JK, Weissman MM, Tischler GL, et al: Six-month prevalence of psychiatric disorders in three communities. Arch Gen Psychiatry 1984; 41:959–967
- Kashani JH, McGee RO, Clarkson, SE, et al: Depression in a sample of 9-year-old children. Arch Gen Psychiatry 1983; 40: 1217-1223
- 8. Rutter M, Graham P, Chadwick OF, et al: Adolescent turmoil: fact or fiction? J Child Psychol Psychiatry 1976; 17:35–56
- Kandel DB, Davies M: Epidemiology of depressive mood in adolescents. Arch Gen Psychiatry 1982; 39:1205–1212
- Kaplan SL, Hong GK, Weinhold C: Epidemiology of depressive symptomatology in adolescents. J Am Acad Child Psychiatry 1984; 23:91–98
- Andreasen NC: Concept, diagnosis and classification, in Handbook of Affective Disorders. Edited by Paykel ES. New York, Guilford Press, 1982
- 12. Herjanic B, Herjanic M, Brown F, et al: Are children reliable reporters? J Abnorm Child Psychol 1975; 3:41-48
- Herjanic B, Reich W: Development of a structured psychiatric interview for children: agreement between child and parent on individual symptoms. J Abnorm Child Psychol 1982; 10:307– 324
- 14. Paul GL, Lentz RJ: Psychosocial Treatment of Chronic Mental Patients. Cambridge, Harvard University Press, 1977
- Keller MB, Shapiro RW: Double depression: superimposition of acute depressive episodes on chronic depressive disorders. Am J Psychiatry 1982; 139:438

  442
- 16. Bartholomew DJ: A test of homogeneity for ordered alterna-

tives. Biometrika 1959; 46:36-48

- 17. Bartholomew DJ: A test of homogeneity for ordered alternatives, II. Biometrika 1959; 46:328-335
- Kashani JH, Carlson GA: Seriously depressed preschoolers. Am J Psychiatry 1987; 144:348-350
- Rutter M: The developmental psychopathology of depression: issues and perspectives, in Depression in Young People. Edited by Rutter M, Izard CE, Read PD. New York, Guilford Press,
- 1986
- Boyd JH, Burke JD, Gruenberg E, et al: Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free syndrome. Arch Gen Psychiatry 1984; 41:983–989
- 21. Akiskal HS, Bitar AH, Puzantian VR, et al: The nosological status of neurotic depression: a prospective three-to-four-year examination in light of the primary-secondary and unipolar-bipolar dichotomies. Arch Gen Psychiatry 1978; 35:756–766

## L-Dopa Challenge and Relapse in Schizophrenia

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Neuroleptic administration has been shown to be superior to placebo in prolonging schizophrenic remission. However, individual patients are able to maintain long periods of remission in the absence of neuroleptic treatment, while others relapse soon after neuroleptic withdrawal. This study attempted to predict time to relapse in 28 schizophrenic patients withdrawn from neuroleptics and challenged with L-dopa for 7 days, then followed until relapse. Time to relapse correlated significantly with L-dopa-induced increase in BPRS score (p=.006). Five of six patients who responded to L-dopa relapsed within 4 weeks after L-dopa administration, while only four of 22 who did not respond relapsed in a comparable period.

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S chizophrenia is a chronic disorder, with most patients attaining a state of remission, only to relapse at a later time. Both reaching and maintaining a remission are facilitated by neuroleptics (1). Unfortunately, chronic neuroleptic administration has potentially irreversible adverse effects such as tardive dyski-

distinguish between patients who, on withdrawal of neuroleptic medication, will experience a rapid relapse and those who can maintain a prolonged state of remission without medication would greatly assist the clinician in this assessment.

Several clinical studies in which schizophrenic patients were challenged with indirect dopamine agonists like amphetamine (5, 6) or methylphenidate (7) indicated that patients in whom those drugs produced transient symptom activation are more likely to experience rapid relapse than are patients in whom dopaminergic drugs had little or no detrimental effects. These results are consistent with a hypothesis suggesting that

nesia (2) in addition to extrapyramidal side effects (3,

4). On the other hand, frequent schizophrenic relapse

can be painful to the patient and results in deteriora-

tion of an already damaged social network. These considerations call for a careful assessment of the

benefits and risks of neuroleptic maintenance in each

individual patient. A clinical tool that would be able to

This study is an attempt to predict time to relapse in schizophrenic patients withdrawn from neuroleptic medication and challenged with L-dopa for 7 days.

patients who fail to buffer an acute dopaminergic

challenge might be more prone to rapid and frequent

**METHOD** 

Twenty-eight male schizophrenic outpatients participated in this study. Chronic medical illnesses, alcohol and drug abuse, and a history of suicidal behavior were reasons for exclusion from the study. The mean±

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TABLE 1. Characteristics of 28 Schizophrenic Patients Withdrawn From Neuroleptics and Challenged With L-Dopa

						Months	Tota	l BPRS Score	
Patient	Diagnosis	Age (years)	Age at Onset (years)	Number of Hospitalizations	Months in Hospital	Stable Before Neuroleptic Withdrawal	Baseline	Change During 1-dopa Challenge	Weeks From L-Dopa Challenge to Relapse
1	Undifferentiated	31	20	2	42	36	37.5	10.0	9
2	Residual	22	20	4	14	33	32.0	0	10
3	Paranoid	61	33	3	144	180	33.0	1.5	13
4	Not currently ill	23	21	2	7	14	27.0	2.0	12
5	Not currently ill	32	21	3	2	15	29.0	2.0	5
6	Residual	26	18	7	36	36	32.0	2.0	5
7	Residual	27	20	5	36	48	34.5	6.5	2
8	Paranoid	36	28			_	33.5	16.5	0
9	Residual	39	30	5	5	23	33.0	8.5	19
10	Residual	40	24	9	11	60	39.5	0.5	3
11	Residual	32				_	26.5	2.0	8
12	Not currently ill	47	28	6	49	84	30.5	2.5	4
13	Not currently ill	49	19	9	28	7	24.0	0.5	34
14	Not currently ill	51	18	12	19	3	25.0	15.0	1
15	Residual	35	29	7	13	10	22.0	16.0	12
16	Paranoid	39	20	8	40	8	44.5	14.5	2
17	Residual	23	21	2	7	3	28.0	5.5	2
18	Paranoid	27	24	5	21	24	30.5	13.5	2 2 2 3
19	Schizoaffective	26	20	5	8	7	24.5	14.0	3
20	Not currently ill	57	32	6	9		23.5	1.5	14
21	Residual	34	21	9	29	14	22.5	10.5	8
22	Undifferentiated	27	22	1	5	49	35.5	4.0	52
23	Residual	23	18	5	12	6	34.5	8.5	17
24	Residual	60	25			8	25.0	3.5	17
25	Residual	42	23	10	30	3	33.0	10.0	1
26	Residual	42	34	3	2	60	23.5	7.0	10
27	Not currently ill	31	26	0	0	14	20.5	3.0	15
28	Residual	41	27	2	2	60	26.5	0	10

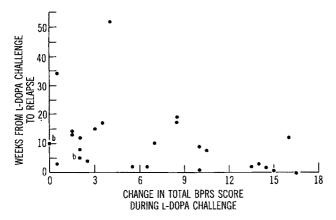
SD age was  $34.7\pm11.1$  years (range=22-61). The diagnosis of schizophrenia was assigned after a Schedule for Affective Disorders and Schizophrenia (SADS) (8) interview was conducted by two raters who observed the same interview. The kappa coefficient correlation between the two raters for the Research Diagnostic Criteria (RDC) (9) was 0.86. Throughout the study, severity of symptoms was assessed by two independent, reliable raters (intraclass correlation= 0.95) with the Brief Psychiatric Rating Scale (BPRS) (10). Seven patients met the RDC for "not currently mentally ill" and had a past diagnosis of schizophrenia, 14 patients met the criteria for residual schizophrenia, and an additional seven met the criteria for other subtypes of schizophrenia but by clinical judgment and past history were in a state of remission as contrasted with their periods of acute exacerbation (see table 1). Patients were judged to be in a "stable" period of relative remission if they 1) had lived in the community without hospitalization for at least 3 months before entering the study and 2) had BPRS scores that were within 12 points of each other during four weekly ratings performed before neuroleptic withdrawal. The mean±SD BPRS score for the 28 patients was  $30.0\pm6.0$ .

After a full explanation of the study, including the risks of neuroleptic discontinuation and L-dopa administration, all patients gave informed consent to participate in the study. Patients were told that during

different stages of the study they would receive fluphenazine or fluphenazine placebo. Hence, throughout the study the investigator knew that the patients were receiving placebo, but the patients were unsure. At least 8 weeks before L-dopa administration patients were placed on a regimen of fluphenazine equivalent to that of their prior neuroleptic; the regimen was changed to fluphenazine placebo for the last 4 weeks before L-dopa challenge. Stability ratings with the BPRS were performed at weekly intervals throughout the 8 weeks before L-dopa challenge, and patients who had an increase in BPRS scores exceeding 12 points between any 2 weeks were considered unstable and excluded from the study.

All patients were admitted to the Special Treatment Unit of the Bronx Veterans Administration Medical Center at least a week before L-dopa administration. The L-dopa challenge consisted of administering L-dopa and carbidopa, 250 mg and 25 mg, respectively, four times a day for 7 days to patients who had been neuroleptic free for a mean of 30 days. BPRS scores were obtained on days 3, 6, and 7 during the L-dopa challenge. The criteria for "positive response" to L-dopa were arbitrarily preestablished as a 12-point increase in total BPRS score. Patients in whom L-dopa produced no change in BPRS score or a change lower than 12 points were considered "negative responders." Change in positive schizophrenic symptoms during the L-dopa challenge was determined by summing the

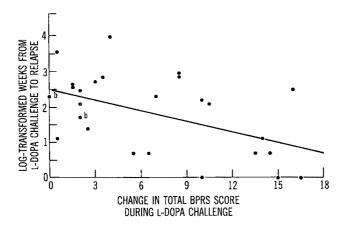
FIGURE 1. Time to Relapse and Change in Total BPRS Score of 28 Schizophrenic Patients Withdrawn From Neuroleptics and Challenged With L-Dopa<sup>a</sup>



<sup>&</sup>lt;sup>a</sup>Significant correlation between change in BPRS score and weeks to relapse (r=-.339, p=.078).

<sup>b</sup>Dot represents two patients.

FIGURE 2. Log Time to Relapse and Change in Total BPRS Score of 28 Schizophrenic Patients Withdrawn From Neuroleptics and Challenged With L-Dopa<sup>a</sup>



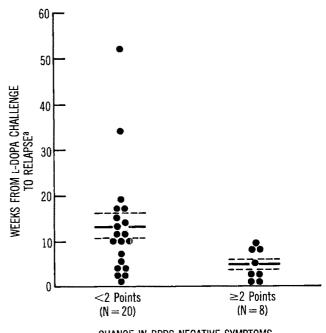
<sup>&</sup>lt;sup>a</sup>Significant correlation between change in BPRS score and logtransformed weeks to relapse (r=-.510, p=.006).

<sup>b</sup>Dot represents two patients.

changes in the item scores of factors 3, 4, and 5 of the BPRS. These factors consist of the following: thought disturbance (conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content), activation (tension, mannerisms, posturing, and excitement), and hostile suspiciousness (hostility, suspiciousness, and uncooperativeness). Change in negative schizophrenic symptoms was determined by summing the changes in the BPRS items of emotional withdrawal, blunted affect, and motor retardation.

After L-dopa challenge, patients were discharged into the community on a regimen of fluphenazine placebo and were rated at weekly intervals for 52 weeks or until they relapsed. The raters were blind to the results of the L-dopa challenge. Relapse was de-

FIGURE 3. Prediction of Time to Relapse by Change in BPRS Negative Symptom Score for 28 Schizophrenic Patients Withdrawn From Neuroleptics and Challenged With L-Dopa



CHANGE IN BPRS NEGATIVE SYMPTOMS DURING L-DOPA CHALLENGE<sup>b</sup>

<sup>a</sup>Bars indicate mean±SE.

bSignificant difference in relapse between the two groups of subjects (t=2.71, df=24.13, p=.01).

fined as 1) an increase in BPRS score of at least 12 points on two consecutive weekly ratings or 2) an increase in BPRS score of at least five points on two consecutive weekly ratings and the opinion of the treating psychiatrist that inpatient care was required.

#### **RESULTS**

Figure 1 illustrates the significant relationship between the greatest total BPRS change during the Ldopa challenge and weeks to relapse after the challenge. As apparent from figure 1, only two subjects did not relapse during the first 20 weeks of the study. Because of the lack of linearity of the relationship between time to relapse and temporary symptomatic worsening during L-dopa challenge, and due to the nonnormal distribution of the data, log-transformation of weeks to relapse was performed and the relationship between time to relapse and change in BPRS score during L-dopa challenge was recalculated. The resultant negative correlation between total BPRS change during the challenge and log-transformed weeks to relapse, as shown by figure 2, was quite robust.

Negative responders (N=22), subjects in whom L-dopa did not produce an increase in total BPRS score of at least 12 points, remained drug free and stable

without requiring hospitalization for a mean  $\pm$  SD of 12.1 $\pm$ 11.5 weeks, while positive responders (N=6), in whom L-dopa did produce an increase of at least 12 points, relapsed in a mean of 3.3 $\pm$ 4.4 weeks (t=-2.90, df=22.62, p=.008). A Fisher's exact test revealed that negative responders to L-dopa were significantly more likely than positive responders to remain stable in remission for 8 weeks or longer (p=.036) or 4 weeks or longer (p=.006).

Change in negative schizophrenic symptoms during L-dopa challenge, as determined by a sum of the BPRS items measuring emotional withdrawal, blunted affect, and motor retardation, predicted time to relapse. There was a significant negative correlation with logtransformed values of weeks to relapse and change in negative symptom score during the L-dopa challenge (r=-.374, p=.05). Change in negative symptoms was also able to predict time to relapse when analyzed as a dichotomous measure. Subjects whose scores for the three negative-symptom BPRS items increased two points or more during L-dopa challenge (N=8) met the criteria for relapse in a mean ±SD of 4.5 ± 3.4 weeks, while subjects whose negative symptom scores did not increase two points (N=20) did not meet the criteria for relapse until a mean of 12.9 ± 12.4 weeks (see figure 3). In contrast, the L-dopa-induced change in positive symptoms, analyzed as both a continuous and a dichotomous measure, did not demonstrate a significant relationship with time to relapse. Other descriptive measures, such as age, baseline drug-free BPRS total score before L-dopa administration, age at onset, time in hospital, number of hospitalizations, and presence of tardive dyskinesia, as well as phenomenological variables, were not related to time to relapse.

#### **DISCUSSION**

A 12-point change on the BPRS scale any time during the 1-week course of L-dopa administration was an accurate prognostic indicator of the likelihood of relapse over the next 4 weeks. Of the 28 patients, 23 were correctly classified. Five of six patients who experienced a 12-point increase while receiving L-dopa relapsed within 4 weeks from the time of L-dopa administration, whereas only four of 22 patients whose increase in the BPRS score was less than 12 points relapsed in a comparable period. Although the ability of the L-dopa trial to predict relapse over a subsequent 8-week period was somewhat less than for 4 weeks, it nonetheless reached a statistically significant level with 20 correct classifications. However, beyond 8 weeks the L-dopa trial was no real guide as to the patient's prognosis.

It was somewhat surprising to note that L-dopa increased negative symptoms. In fact, like the total BPRS score, change in negative symptoms, but not in positive symptoms, correlated with the log of weeks to relapse. The most simplistic explanation for these observations is that with exacerbation of positive

symptoms, there was a secondary worsening in negative symptoms. However, the possibility that augmenting dopaminergic activity can worsen negative symptoms, as a primary and not a secondary event, is intriguing and underlies a general ignorance about the relationship between dopaminergic neurotransmission and symptoms.

An acute challenge with amphetamine (5, 6) or methylphenidate (7) has also been used to predict the time of relapse of schizophrenic patients in a drug-free state. This acute challenge strategy has been better able to predict patients who would do poorly than patients who would do well (5). In contrast, at least through 4 weeks after a 1-week challenge with L-dopa, the Ldopa-induced change in the BPRS score was approximately equal in predicting good and poor prognosis. Perhaps this somewhat greater accuracy of L-dopa can be accounted for by its more specific involvement in the dopaminergic metabolism in comparison to amphetamine and amphetamine-like compounds. Furthermore, the chronic administration of L-dopa, versus a single challenge with amphetamine, might have increased the predictive power of the L-dopa test.

Some aspects of this study were not ideal. Neuroleptics were discontinued on a single-blind basis, with staff being aware of when fluphenazine placebo was substituted for fluphenazine. In addition, both patients and staff were cognizant of when L-dopa was being administered. The intense scrutiny that patients underwent during the week-long L-dopa trial may have added to their anxiety and been reflected in the BPRS scale. Thus, in a very real sense, patients were being challenged not only by L-dopa but by an artificially induced stressful situation. It is impossible to ascertain whether this additional nonpharmacologica! factor increased or decreased the precision of the 12-point BPRS change to predict subsequent relapse.

The vast majority of patients returned to baseline levels of psychopathology, as assessed by the BPRS scale, after the discontinuation of L-dopa. However, a few patients did not, and indeed their relapse could be said to have begun concomitant with L-dopa administration and continued with the discontinuation of the drug. It seems likely that L-dopa played a role in bringing on relapse in these few patients or caused some form of sensitization to psychosis. However, without a placebo L-dopa group it is impossible to know how many patients would have relapsed during this time period had L-dopa not been administered.

The rate of tardive dyskinesia in patients who have received chronic neuroleptics for over a year is estimated at approximately 3% per year (11). The expression of these abnormal involuntary movements is the major detriment to the otherwise beneficial use of neuroleptics in the acute and chronic treatment of schizophrenia. Thus, strategies that can predict the likelihood of relapse in a drug-free period have obvious utility. Results from the present study indicate that for at least 4 weeks, beginning with a 1-week 1-dopa trial, the course of patients can be reasonably well

estimated and that acceptable levels of accuracy may even exist for an 8-week period. However, further refinements in this approach will be needed before a pharmacological challenge could be considered to guide neuroleptic withdrawal.

- 1. Klein D, Davis J: Diagnosis and Drug Treatment of Psychiatric
- Disorders. Baltimore, Williams & Wilkins, 1969, pp 52–138

  2. Jeste DV, Wyatt RJ: Understanding and Treating Tardive Dyskinesia. New York, Guilford Press, 1982, pp 81-106
- 3. Rifkin A, Quitkin F, Klein DF: Akinesia: a poorly recognized drug-induced extra-pyramidal behavior disorder. Arch Gen Psychiatry 1975; 32:672-674
- 4. Van Putten T, May PRA: "Akinetic depression" in schizophrenia. Arch Gen Psychiatry 1976; 33:231–239
- 5. Angrist B, Peselow E, Rubinstein M, et al: Amphetamine

- response and relapse risk after depot neuroleptic discontinua-
- tion. Psychopharmacology 1975; 85:277-283
  6. van Kammen DP, Docherty JP, Bunney WE: Prediction of early relapse after pimozide discontinuation by response to d-amphetamine during pimozide treatment. Biol Psychiatry 1982; 17:223-242
- 7. Lieberman JA, Kane JM, Gadaleta D, et al: Methylphenidate challenge as a predictor of relapse in schizophrenia. Am J Psychiatry 1984; 141:633-638
- 8. Endicott J, Spitzer RL: A diagnostic review: The Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837-844
- 9. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
- 10. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799-812
- 11. Kane JM, Woerner M, Lieberman JA, et al: Tardive dyskinesias. Drug Development Research 1986; 9:41-51

# Athletic Amenorrhea, Major Affective Disorders, and Eating Disorders

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While studying amenorrheic runners, the authors became aware of psychiatric differences between them. Psychiatric interviews of 13 amenorrheic and 19 regularly menstruating runners revealed that of the amenorrheic runners, 11 reported major affective disorders in themselves or in first- and second-degree relatives and eight reported eating disorders in themselves. Among the regularly menstruating runners, however, there were no eating disorders or major affective disorders, and only one had first-degree relatives with major affective disorders. These data suggest a link between athletic amenorrhea in runners, major affective disorders, and eating disorders.

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In a study of the diets of amenorrheic and regularly I menstruating long-distance runners (1), we were struck by the obsessive preoccupation with diet in the amenorrheic subjects. The amenorrheic runners also seemed more prone to emotional disturbance if anything interfered with their running regimen than did their regularly menstruating counterparts. We perceived a possible parallel between athletic amenorrhea and anorexia nervosa, with its secondary amenorrhea and preoccupation with diet and minimal body weight, as potentially relevant to the runners' secondary amenorrhea. Some male "obligatory runners" have been shown to have psychological profiles similar to those of women with anorexia nervosa (2). Preliminary psychiatric evaluation of a few amenorrheic and regular runners serendipitously revealed major affective disorders in the amenorrheic runners and their families as well as frank eating disorders in themselves. The more extensive study reported here was designed to explore the nature and extent of psychiatric differences between the two groups rather than to test preexisting hypotheses.

#### **METHOD**

Our subjects were 13 amenorrheic and 19 regularly menstruating runners. They were paid volunteers recruited from the Boulder/Denver area, and informed consent was obtained from each subject. Requirements were that they ran at least 35 miles/week, had never borne a child, and had not taken oral contraceptives within the 6 months before the study. To qualify as regularly menstruating, they must have had 12 periods/year lasting for 3–7 days at 23–33-day intervals. To qualify for the amenorrheic group, they must have had a history of regular menstrual cycles that were established within 18 months following menarche, training that had begun before amenorrhea developed, not more than three periods/year, and not more than one period in the 6 months before the study.

The obvious difficulty in obtaining an adequate number of subjects meeting such rigid criteria precluded selection of specifically matched control subjects; no volunteers who met the criteria were excluded. Rigorous inclusion of all qualified subjects obviated selection bias for psychiatric profile.

All subjects were interviewed by a psychiatrist (W.J.G.) for 90 minutes. Interviews were structured to include menstrual history; personal and family history of medical and psychiatric illness; family, social, and marital relationships; running history and its personal meaning; dietary status; and self-concepts. The majority of the interviews were tape-recorded and independently reviewed by a second investigator (W.W.W.). The subjects were the sole informants. The interviews were of sufficient depth to permit a diagnostic impression of each subject; DSM-III criteria were used. Regarding family history of psychiatric conditions, when the subject could describe a relative's behavior and symptoms on the basis of personal observation in sufficient detail to meet DSM-III criteria, a presump-

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TABLE 1. Characteristics of 13 Amenorrheic Runners and 19 Regularly Menstruating Runners

	Amenorrheic Runners		Regularly Menstruating Runners		Analysis of Variance		
Characteristic	Mean	\$D	Mean	SD	F	df	р
Current age (years)	25.5	5.5	28.8	5.4	2.86	1, 30	>.05
Age at menarche (years)	13.4	1.7	13.9	2.0	0.48	1, 29	>.05
Miles run/week	45.1	7.7	47.8	10.4	0.62	1,30	>.05
Weight (kg)	49.1	3.9	53.9	4.5	7.39	1, 25	<.05
Height (cm)	162.4	5.6	161.8	8.8	0.03	1, 25	>.05
Body fat (%)	15.8	4.2	18.1	5.0	1.46	1, 25	>.05

TABLE 2. Eating Disorders, Major Affective Disorders, and Family History in 13 Amenorrheic Runners and 19 Regularly Menstruating Runners

	Amenorrheic Runners		Regularly Menstruating Runners		Chi-Square Analysis		
Variable	N	%	N	%	X <sup>2</sup>	df	p
Eating disorders	8	62	0	0	12.48	1	<.001
Bipolar disorder or major depression First- or second-degree relatives with major	3	23	0	0	2.50	1	>.05
affective disordera	10	77	1	5	14.54	1	<.001

<sup>&</sup>lt;sup>a</sup>The 13 amenorrheic runners reported on 71 first- and 49 second-degree relatives; the 19 regularly menstruating runners reported on 85 first- and 69 second-degree relatives.

tive diagnosis was made. At times the subject knew of a relative's diagnosis and some details of treatment such as psychiatric treatment modalities, hospitalizations, and medications. To make a presumptive diagnosis of a major affective disorder, either the reported diagnosis or the subject's description had to include at least one of the following criteria: psychiatric hospitalization with treatment by antidepressants, lithium, or ECT; prolonged outpatient treatment with antidepressants, lithium, or ECT; suicide or suicide attempts arising out of symptoms of a major affective disorder; or incapacitation in the context of such symptoms and treatment.

Percent body fat was measured by using underwater weighing. The weight of each subject was determined in air (Wa) on a beam scale accurate to 100 g (Accu-weigh). The subjects exhaled maximally to residual volume while submerged underwater. Their weight underwater (Ww) was measured with a Chatilon scale accurate to 10 g. The mean of the last three of 10 trials was accepted as the underwater weight (3). Preceding the underwater weighing, pulmonary residual volume (RV) was determined with a nitrogen analyzer (Hewlett Packard Model 4720A) by using the method of Wilmore (4). The average of two trials was used in the calculations. None of the subjects had exercised for at least 8 hours or had eaten for at least 4 hours before the test.

By accounting for subjects' water density (Dw), their body density (5) was calculated by using the following equation:

Body density (g/ml) = Wa/[(Wa - Ww/Dw) - RV].

From body density, percent body fat (6) was calculated by using the following equation:

Percent body fat= $[(4.570/body density)-4.142]\times 100$ .

Lean body weight was computed by using the following equation:

Lean body weight=body weight-fat weight.

Analysis of variance was used to determine the differences between the characteristics of the regularly menstruating and amenorrheic runners. Chi-square tests  $(2\times2)$  were used to determine the differences between the incidences of personal and family history of major affective disorders and of eating disorders of the regularly menstruating and amenorrheic runners. Statistical significance was set at p<.05.

#### **RESULTS**

The regularly menstruating group and the amenorrheic group were not statistically different in age, age at menarche, miles of training/week, and height (table 1). Although there was a significant difference in body weight between the two groups, the percentage of body fat was similar (table 1).

The results we report here are restricted to the incidence of personal and family history of major affective disorders and of eating disorders. Table 2 indicates that the rate of major affective disorders in amenorrheic runners and in their first- and second-degree relatives and the rate of eating disorders in the

runners were significantly higher than they were in the control subjects or their relatives. It is interesting to note that the rates of major affective disorders in the two groups of runners themselves did not reach statistical significance. However, it was only among the amenorrheic runners that there were any diagnoses of major affective disorder (23%).

#### DISCUSSION

There are obvious limitations to this preliminary study. The numbers of subjects and control subjects were limited by the stringent selection criteria, but the groups were large enough to permit statistical comparison. Subjects and control subjects were not purposely matched, but analysis revealed that matching was indeed obtained. All interviewing was done by a single investigator who was exploring all aspects of personal and family history; he was not blind to subjects' menstrual or dietary history while pursuing further information about the subject herself or her family. Since the study's purpose was to explore the possibility of links between various disorders and to develop rather than to test hypotheses, blindness could not be a part of such a design. Bias in the pursuit and interpretation of data could well have intruded as correlations began to appear, despite efforts to remain objective. Replicative studies could be designed to correct for any such bias. Another potential source of error is that the relatives themselves were not interviewed, and no objective data such as medical records were obtained. All family history data were gathered from the subjects. However, the family history method has been shown to underestimate the incidence of psychiatric illness in family members when compared with direct interviewing of family members (7–9). Therefore, if the findings of this study are in error, the true prevalence of major affective disorders in family members is likely to be higher rather than lower than that reported here.

The clustering of eating disorders and major affective disorders in amenorrheic runners and their virtual absence in regularly menstruating control subjects raises some interesting speculations. Amenorrhea is an essential feature of anorexia nervosa but does not always occur in bulimia. There is considerable evidence linking eating disorders with major affective disorders. There is a statistically significant incidence of major affective disorders in family members of anorexic patients (10–13), and a follow-up study of anorexic patients (14) found that at least 40% were diagnosed as having a major affective disorder of the depressive type. Major affective disorders and anorexia nervosa have significant correlations between shared genetic markers (14), disturbances of endocrine function and neurotransmitter metabolites (15–21), and EEG sleep disorders and sleep recordings (22, 23). Chemotherapy that is effective in the major affective disorders has also been successful in the treatment of a substantial number of anorexic and bulimic patients (24–27). There is some indication that bulimic patients more frequently show depressive symptoms (28–30).

In addition to the finding of a diagnosable eating disorder in 62% of the amenorrheic runners, contrasted with none in the regularly menstruating runners, there are several other parallels between the amenorrheic group and patients with anorexia nervosa-e.g., low food intake, ritualized dietary habits, heightened energy and activity, secondary amenorrhea, and compulsive behavior. The fact that 12 of the 13 amenorrheic runners were vegetarians, compared with only three vegetarians among the 19 regularly menstruating runners, is a further instance of atypical eating patterns in the amenorrheic group (1). Although the amenorrheic runners appeared thin, their mean± SD weight (49.1±3.9 kg) was surprisingly high for their height (162.4±5.6 cm); this body weight came from a high lean mass of 41.3±3 kg. If they had not developed such musculature from their heavy training schedules, they would have been expected to weigh substantially less and thereby display the more emaciated appearance associated with anorexia.

It is possible that at least a subset of amenorrheic runners represents a variant of anorexia nervosa and/ or major affective disorder, given the significant correlation found in this study among these three conditions. (Although secondary amenorrhea is by definition a symptom of anorexia nervosa, its relevance in affective disorders has not been shown.) A further possibility is that compulsive running among the amenorrheic subjects is a defense, not always successful, against one of the other disorders. Running has been shown to ameliorate psychogenic depression (31), perhaps through endorphin release (2, 32). Fifty-four percent of the amenorrheic group reported becoming severely dysfunctional, with symptoms of depression and agitation, when unable to run, contrasted with 5% of the control group. A still further speculation is that some proportion of cases of athletic amenorrhea, eating disorders, and major affective disorders may constitute a spectrum of clinically, biologically, and genetically related conditions associated with monoamine disorders of the CNS.

The speculations arising from the data of this study are amenable to testing. For example, athletic amenorrhea may, like a substantial portion of eating disorders, respond to the accepted pharmacotherapy of affective disorders. The distress of amenorrheic runners who want children, the life- and health-threatening severity of eating disorders and of the major affective disorders for which they may be at greater than expected risk, and the frequency of media and anecdotal reports of suicide among driven, compulsive runners suggest that this condition may not be simply a benign, incidental side effect of intense training.

#### REFERENCES

1. Brooks SM, Sanborn CF, Albrecht BH, et al: Diet in athletic amenorrhea. Lancet 1984; 2:559-560

- 2. Yates A, Leehey K, Shisslak CM: Running—an analogue to anorexia? N Engl J Med 1983; 308:251-255
- Katch F, Michael ED, Horvath S: Estimation of body volume by underwater weighing: description of a simple method. J Appl Physiol 1967; 23:811-813
- 4. Wilmore JH: A simplified method for determination of residual lung volumes. J Appl Physiol 1969; 27:96–100
- 5. Keys A, Brozek J. Body fat in adult man. Physiol Rev 1953; 33:245-325
- Brozek J, Gramde F, Anderson JT, Keys A: Densiotometric analysis of body composition: revision of some quantitative assumptions. Ann NY Acad Sci 1963; 110:113–140
- Mendlewicz J, Fliess JL, Cataldo M, et al: Accuracy of the family history method in affective illness. Arch Gen Psychiatry 1975; 32:309–314
- Andreasen NC, Endicott J, Spitzer RL, et al: The family history method using diagnostic criteria. Arch Gen Psychiatry 1977; 34:1229–1235
- Thompson WD, Orvaschel H, Prusoff BA, et al: An evaluation of the family history method for ascertaining psychiatric disorders. Arch Gen Psychiatry 1982; 39:53-58
- Cantwell DP, Sturzenberger S, Burroughs J, et al: Anorexia nervosa: an affective disorder? Arch Gen Psychiatry 1977; 34:1087–1093
- Winokur A, March V, Mendels J: Primary affective disorder in relatives of patients with anorexia nervosa. Am J Psychiatry 1980; 137:695-698
- Hudson JI, Pope HG Jr, Jonas JM, et al: Family history study of anorexia nervosa and bulimia. Br J Psychiatry 1983; 142:133– 138
- Gershon ES, Hamovit JR, Schreiber JL, et al: Anorexia nervosa and major affective disorders associated in families: a preliminary report, in Childhood Psychopathology and Development. Edited by Guze SB, Earls FJ, Barrett JE. New York, Raven Press, 1983
- Biederman J, Rivinus TM, Herzog DB, et al: High frequency of HLA-Bw16 in patients with anorexia nervosa. Am J Psychiatry 1984; 141:1109–1110
- 15. Walsh BT: Endocrine disturbances in anorexia nervosa and depression. Psychosom Med 1982; 44:85-91
- Gwirtsman HE, Gerner RH: Neurochemical abnormalities in anorexia nervosa: similarities to affective disorders. Biol Psychiatry 1981; 16:991–995
- 17. Gwirtsman HE, Roy-Byrne P, Yager J, et al: Neuroendocrine

- abnormalities in bulimia. Am J Psychiatry 1983; 140:559-563 18. Hudson JI, Laffer PS, Pope HG Jr: Bulimia related to affective
- disorder by family history and response to the dexamethasone suppression test. Am J Psychiatry 1982; 139:685–687
- Gerner RH, Gwirtsman HE: Abnormalities of dexamethasone suppression test and urinary MHPG in anorexia nervosa. Am J Psychiatry 1981; 138:650-653
- Halmi KA, Dekirmenjian H, Davis JM, et al: Catecholamine metabolism in anorexia nervosa. Arch Gen Psychiatry 1978; 35:458–460
- Gross HA, Lake CR, Ebert MH, et al: Catecholamine metabolism in primary anorexia nervosa. J Clin Endocrinol Metab 1979; 49:805–809
- Nell JF, Merikangas JR, Foster FG, et al: Waking and all-night sleep EEG's in anorexia nervosa. Clin Encephalogr 1980; 11:9-15
- Katz JL, Kuperberg A, Pollack CP, et al: Is there a relationship between eating disorder and affective disorder? new evidence from sleep recordings. Am J Psychiatry 1984; 141:753-759
- Moore DC: Amitriptyline therapy in anorexia nervosa. Am J Psychiatry 1977; 134:1303–1304
- Gross HA, Ebert MH, Faden VB, et al: A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. J Clin Psychopharmacol 1981; 1:376–381
- Walsh BT, Stewart JW, Wright L, et al: Treatment of bulimia with monoamine oxidase inhibitors. Am J Psychiatry 1982; 139:1629-1630
- Pope HG Jr, Hudson JI, Jonas JM, et al: Bulimia treated with imipramine: a placebo-controlled double-blind study. Am J Psychiatry 1983; 140:554–558
- Garfinkel PE, Moldofsky H, Garver DM: The heterogeneity of anorexia nervosa: bulimia as a distinct subgroup. Arch Gen Psychiatry 1980; 37:1036–1040
- Casper RC, Eckert ED, Halmi KA, et al: Bulimia: its incidence and clinical importance in patients with anorexia nervosa. Arch Gen Psychiatry 1980; 37:1030–1035
- Strober M: The significance of bulimia in juvenile anorexia nervosa: an exploration of possible etiologic factors. Int J Eating Disorders 1981; 1:28–43
- 31. Greist JH, Klein MH, Eischens RR, et al: Running as treatment for depression. Compr Psychiatry 1979; 20:41-54
- 32. Kaye WH, Pickar D, Naber D, et al: Cerebrospinal fluid opioid activity in anorexia nervosa. Am J Psychiatry 1982; 139:643-645

# Absence of Carbamazepine-Induced Hyponatremia Among Patients Also Given Lithium

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Of 33 chronically psychotic patients in a state hospital, 17 received carbamazepine, 13 received carbamazepine and lithium, and three received carbamazepine and then the combination. There was a significant difference in serum sodium level between the patients receiving carbamazepine alone (mean±SD=138.4±4.3 meq/liter) and those also receiving lithium (141.8±1.6 meq/liter). (A similar difference was seen for the patients who received the two treatments serially.) Age, sex, diagnosis, age at diagnosis, seizure disorder, antipsychotic drugs, and serum carbamazepine level did not explain this difference. The protection against hyponatremia provided by the carbamazepine-lithium combination occurred despite lithium's tendency to increase polyuria.

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S ince the introduction of carbamazepine to clinical medicine in 1962, multiple applications have evolved, including treatment of patients with trigeminal neuralgia, CNS injury, dystonic disorders, partial complex seizures, generalized seizures, interictal personality disorders, psychosis, paraphilias, various affective states (including bipolar disorder), chronic pain syndromes, impulse dyscontrol, and diabetes insipidus (1–9). Multiple reports implicating carbamazepine in the syndrome of inappropriate antidiuresis have also appeared (10–14).

Our recent interest in patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome) (15–32) has stimulated us to look for various causes of hyponatremia among institutionalized chronically psychotic patients. In our search for causes we have also sought treatments for hyponatremia. Since lithium has

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been used effectively to treat patients with the syndrome of inappropriate antidiuresis (33, 34) as well as patients with various affective states, we reviewed the serum sodium and urinary specific gravity measurements of a group of institutionalized chronically psychotic patients who received carbamazepine and a group who received a combination of carbamazepine and lithium. The latter group had fewer episodes of hyponatremia and a higher mean serum sodium level than the former group. The clinical implications of our findings are discussed.

#### **METHOD**

We reviewed the hospital charts in one of the chronic care units at Western State Hospital for the period January to December 1984. From the 120 charts reviewed, 33 patients were found who had at least three simultaneously obtained measurements of serum sodium and carbamazepine levels. Of these 33 patients, 17 received carbamazepine, 13 received carbamazepine and lithium, and three received carbamazepine and then the combination of carbamazepine and lithium. DSM-III criteria were used to establish the diagnoses. The distributions of diagnoses and sex were similar in the first two groups; the spectrum of diagnoses included organic affective disorder, schizoaffective disorder, major depression with psychosis, and bipolar disorder (manic-depressive illness). The indications for drug administration included these diagnoses plus generalized seizures and partial complex seizures. The prevalence of seizure disorders was similar in the two groups.

The information obtained about each patient included age, sex, diagnosis, age at diagnosis, presence or absence of seizures, medicines received, serial simultaneous measurements of serum sodium and carbamazepine levels, and the lowest early morning urinary specific gravity. All patients had been treated with carbamazepine or carbamazepine plus lithium for at least 2 weeks before determination of the serum sodium and carbamazepine levels used in our statistical analysis. Fluorescence polarization was the method used for carbamazepine level determinations (35). For

the 16 patients receiving lithium, the serum values ranged between 0.6 and 1.2 meq/liter. All 33 patients received antipsychotic drugs during the course of this study. There was no significant difference in mean± SD chlorpromazine equivalency levels between the patients receiving carbamazepine alone (2143±1922 mg/day) and those receiving carbamazepine and lithium (2027±1749 mg/day).

Correlations among age, age at diagnosis, urinary specific gravity, serum sodium level, and serum carbamazepine level were sought with the Pearson product-moment correlation coefficient. Differences between group means were examined with the unpaired t statistic. Differences between the mean values for the three patients who received carbamazepine then carbamazepine plus lithium were examined with the paired t statistic.

#### RESULTS

There was no correlation between simultaneously measured serum sodium and carbamazepine levels for the patients who received carbamazepine alone (r=-.112) or those who received carbamazepine plus lithium (r=.085) (table 1). This observation also held true for the three patients who received carbamazepine and then carbamazepine plus lithium (table 2).

There was no significant difference (unpaired t statistic) between the patients who received carbamazepine alone and those who received the carbamazepinelithium combination in age (t=-0.454, df=28, p> .50), age at diagnosis (t=0.044, df=28, p>.5), or serum carbamazepine level (t=-1.126, df=28, p= .269) (table 1). There was a tendency for polyuria to increase (t=1.675, df=28, p=.102) during lithium coadministration; the mean urinary specific gravity values for the two groups were 1.014 and 1.010, respectively. However, there was a clear difference (t=-2.803, df=28, p=.009) in serum sodium levels between the two groups. For the patients receiving carbamazepine only, individual serum sodium levels as low as 113 meg/liter were recorded and were associated with generalized seizures. For the patients receiving carbamazepine and lithium, individual serum sodium levels as low as 132 meg/liter were recorded.

Table 2 shows the mean serum sodium and carbamazepine levels of the three patients who received carbamazepine and then carbamazepine plus lithium. The mean values for urinary specific gravity during the two treatments were  $1.012\pm0.008$  and  $1.008\pm0.001$ , respectively. There was a difference (t=-6.269, df=2, p=.021) between the serum sodium levels during the two treatments.

#### DISCUSSION

Our data demonstrate that chronically psychotic patients receiving the combination of carbamazepine

TABLE 1. Serum Sodium and Carbamazepine Levels of Chronically Psychotic Patients Treated with Carbamazepine or Carbamazepine Plus Lithium

Patient	Age (years)	Sex	Mean Serum Sodium Level (meq/liter)	Mean Serum Carbamazepine Level (μg/ml)
Carbamazepine				
alone	**	-	424.5	
1	59 20	F	131.5	6.8
2 3	30	M	131.5	5.7
	58	F	131.8	9.7
4 5	45	M	133.3	8.4
2	24	M	133.6	7.1
6 7	29	M	137.6	6.6
7	41	M	138.9	7.6
8	37	F	139.9	10.5
9	34	M	140.3	6.8
10	29	M	140.6	6.0
11	30	M	140.9	5.2
12	28	M	141.1	7.7
13	27	M	141.7	7.2
14	34	M	142.0	6.9
15	33	M	142.2	7.5
16	26	F	142.3	7.5
17	34	M	143.1	6.9
Mean	35.2		138.4	7.3
Carbamazepine				
plus lithium	•		4000	
18	34	M	138.9	7.4
19	29	M	139.7	5.5
20	34	M	140.7	8.5
21	27	F	140.8	9.6
22	26	M	141.0	7.7
23	33	M	142.0	11.5
24	44	M	142.0	7.1
25	25	M	142.1	6.7
26	62	F	142.4	9.3
27	26	M	142.9	6.6
28	55	F	143.1	8.6
29	55	F	144.0	6.4
30	32	M	144.2	7.8
Mean	37.1		141.8	7.9

and lithium have a higher mean serum sodium level than chronically psychotic patients receiving carbamazepine alone. Age, sex, diagnosis, age at diagnosis, seizure disorder, antipsychotic drugs, urinary specific gravity, and serum carbamazepine level did not explain this difference.

Recently, several investigators (36, 37) have tried to assess systematically the capacity of carbamazepine to induce hyponatremia. Uhde and Post (36) reported on 12 patients receiving placebo and then carbamazepine. There was a drop (p<.01) in serum sodium level from 141.3 meq/liter (placebo) to 139.0 meq/liter (carbamazepine). It is important that carbamazepine's capacity to induce hyponatremia was dose related. Lahr (37) found a mean serum sodium level of 138.8 meq/liter among 60 patients receiving carbamazepine and a mean level of 141.7 meq/liter among 61 age-matched control subjects (p<.001). Again, there appeared to be a relationship between higher serum levels of carbamazepine and hyponatremia.

The mechanism by which carbamazepine induces hyponatremia remains controversial. In a study of six

9.4

8.6

		Carba	mazepine	Carbamazepine Plus Lithium		
Patient	Age (years)	Sex	Mean Serum Sodium Level (meq/liter)	Mean Serum Carbamazepine Level (µg/ml)	Mean Serum Sodium Level (meq/liter)	Mean Serum Carbamazepine Level (µg/ml)
1	39 24	M	133.7	8.3	139.3	10.1

7.5

134.9

134.1

TABLE 2. Serum Sodium and Carbamazepine Levels of Three Chronically Psychotic Patients Treated With Carbamazepine and Then Carbamazepine Plus Lithium

patients with neurogenic (central) diabetes insipidus, Meinders et al. (38) concluded that this drug achieves its antidiuretic effect either by directly affecting the distal renal tubular cell or by enhancing renal sensitivity to the antidiuretic hormone arginine vasopressin. Specifically, they were persuaded that carbamazepine does not stimulate the central release of arginine vasopressin. In contrast, Kimura et al. (39) studied four patients with neurogenic diabetes insipidus and found that carbamazepine acted through the release of arginine vasopressin, thereby inducing antidiuresis. Stephens et al. (40) studied 12 healthy young persons who, when given carbamazepine, developed lower concentrations of arginine vasopressin. They believed that this drug induces antidiuresis by increasing renal sensitivity to normal levels of arginine vasopressin. Thomas et al. (41) studied five normal subjects before and during carbamazepine administration. Their data suggested that this drug changes the threshold of the osmoreceptors in the hypothalamus, leading to an abnormal central response to changes in sodium concentration. Gold et al. (42) studied seven patients with bipolar disorder (manic-depressive illness) using hypertonic saline infusion during placebo and carbamazepine administration. There was a reduction in the level of arginine vasopressin, suggesting that this drug enhances renal responsitivity to available arginine vasopressin.

M

25

Mean

29.3

Several investigators (43–45) have employed phenytoin in an effort to reverse carbamazepine-induced hyponatremia. Again, the data are conflicting as to how phenytoin brings about this change. Sordillo et al. (43) contended that phenytoin blocks the central release of arginine vasopressin, thereby reversing antidiuresis and associated hyponatremia. Perucca and Richens (45) reported that the addition of phenytoin led to a reduction in circulating levels of carbamazepine and, thereby, a correction of hyponatremia.

While there is no agreement as to the mechanism by which carbamazepine causes the syndrome of inappropriate antidiuresis, there is a consensus that lithium interferes with arginine vasopressin action in the kidneys, causing nephrogenic diabetes insipidus (33, 34). Thus, there is a clear rationale for the use of lithium among patients with hyponatremia due to carbamazepine administration unless lithium is contraindicated for medical reasons. However, Ghose (46) offered a note of caution about the combination of carbamaze-

pine and lithium. He used carbamazepine to treat 10 patients with affective disorders who had lithium-induced polyuria in an effort to reverse the polyuria. The polyuria was not helped, and there was a high incidence of ataxia, dizziness, restlessness, and confusional states after the addition of carbamazepine. More recently, Shukla et al. (47) corroborated these neurotoxic findings during treatment with the combination of carbamazepine and lithium. While we did not study the potential neurotoxic complications of carbamazepine and lithium in a systematic way, it was our impression that this drug combination was well tolerated clinically.

139.0

Recently, Raskind et al. (48) demonstrated in an elegant study that antipsychotic drug administration did not elevate the arginine vasopressin levels of a group of psychotic patients. That is, antipsychotic drugs did not induce the syndrome of inappropriate antidiuresis. Since the mean chlorpromazine equivalency levels in our study were similar during treatment with carbamazepine and combination treatment, the question of antipsychotic-induced inappropriate antidiuresis is not an issue for our patients.

While lithium reversed hyponatremia in our sample, there was a tendency for polyuria to appear after its addition. The polyuria was not a problem clinically.

The combination of carbamazepine and lithium was used in our sample in an effort to achieve an additive psychoactive effect rather than for their opposing effects on water regulation. In our review we did not assess the potential additive psychoactive effect of these two drugs—although success has been reported with this drug combination in patients with bipolar disorder (49). Furthermore, our sample was a select one and not typical of patients for whom carbamazepine is usually used. Nevertheless, our findings should stimulate further studies of this drug combination and offer clinicians another choice when faced with a patient who requires carbamazepine treatment and has hyponatremia.

- Dalby MA: Behavioral effects of carbamazepine, in Advances in Neurology, vol 2. Edited by Penry JK, Daly DD. New York, Raven Press, 1975
- Hellekson C, Buckland R, Price T: Organic personality disturbance: a case of apparent atypical cyclic affective disorder. Am J Psychiatry 1979; 136:833-835

- 3. Ballenger JC, Post RM: Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 1980; 137:782-790
- 4. Okuma T, Inanaga K, Otsuki S, et al: A preliminary doubleblind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. Psychopharmacology (Berlin) 1981; 73:95-96
- 5. Folks DG, King LD, Dowdy SB, et al: Carbamazepine treatment of selected affectively disordered inpatients. Am J Psychiatry 1982; 139:115-117
- 6. Garbutt JC, Loosen PT: Is carbamazepine helpful in paroxysmal behavior disorders? Am J Psychiatry 1983; 140:1363-1364
- 7. Goldberg RL, Buongiorno PA: The use of carbamazepine for the treatment of paraphilias in a brain damaged patient. Int J Psychiatry Med 1983; 12:275-279
- 8. Mattson RH, Cramer JA, Collins JF, et al: Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl Med 1985; 313:145-151
- 9. Schaffer CB, Mungas D, Rockwell E: Successful treatment of psychotic depression with carbamazepine. J Clin Psychopharmacol 1985; 5:233-235
- 10. Flegel KM, Cole CH: Inappropriate antidiuresis during carbamazepine treatment. Ann Intern Med 1977; 87:722-723
- 11. Ashton MG, Ball SG, Thomas TH, et al: Water intoxication associated with carbamazepine treatment. Br Med J 1977; 1:
- 12. Stephens WP, Espir MLE, Tattersall RB, et al: Water intoxication due to carbamazepine. Br Med J 1977; 1:754-755
- 13. Perucca E, Garratt A, Hebdige S, et al: Water intoxication in epileptic patients receiving carbamazepine. J Neurol Neurosurg Psychiatry 1978; 41:713-718
- 14. Kalff R, Houtkooper MA, Meyer JWA, et al: Carbamazepine
- and serum sodium levels. Epilepsia 1984; 25:390-397 Vieweg WVR, Rowe WT, David JJ, et al: Evaluation of patients with self-induced water intoxication and schizophrenic disorders (SIWIS). J Nerv Ment Dis 1984; 172:552-555
- 16. Vieweg V, Rowe W, David J, et al: Hyposthenuria as a marker for self-induced water intoxication and schizophrenic disorders. Am J Psychiatry 1984; 141:1258-1260
- Vieweg WVR, Rowe WT, David JJ, et al: The "Mini-Mental State" examination in the syndrome of self-induced water intoxication and schizophrenic disorders (SIWIS): a pilot study. Int J Psychiatry Med 1984; 14:347-359
- 18. Vieweg WVR, Rowe WT, David JJ, et al: Oral sodium chloride in the management of schizophrenic patients with self-induced
- water intoxication. J Clin Psychiatry 1985; 46:16-19
  19. Vieweg WVR, David JJ, Rowe WT, et al: Death from selfinduced water intoxication among patients with schizophrenic
- disorders. J Nerv Ment Dis 1985; 173:161-165 20. Vieweg WVR, Rowe WT, David JJ, et al: Patterns of urinary excretion among patients with self-induced water intoxication
- and psychosis. Psychiatry Res 1985; 15:71-79
  21. Vieweg WVR, Rowe WT, David JJ, et al: Possible ameliorating effect of captopril treatment and hyperosmolar coma in a patient with psychosis, intermittent hyponatremia, and polydipsia. Psychiatr Hosp 1985; 16:183–186
- 22. Vieweg WVR, David JJ, Rowe WT, et al: Psychogenic polydipsia and water intoxication—concepts that have failed. Biol Psychiatry 1985; 20:1308-1320
- 23. Vieweg WVR, David JJ, Rowe WT, et al: Correlation of cigarette-induced increase in serum nicotine levels with arginine vasopressin concentration in the syndrome of self-induced water intoxication and psychosis (SIWIP). Can J Psychiatry 1986; 31:108-111
- 24. Vieweg V: Prevention of water intoxication, in CME Syllabus and Scientific Proceedings in Summary Form, 139th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1986
- 25. Vieweg WVR, David JJ, Rowe WT, et al: Lack of changes in urinary excretion among patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome) while receiving the combination of lithium and phenytoin. Psychiatr Hosp 1986; 17:127-131

- 26. Vieweg WVR, David JJ, Rowe WT, et al: Diurnal variation of urinary excretion for patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome). Biol Psychiatry 1986; 21:1031-1042
- 27. Vieweg WVR, Yank GR, Rowe WT, et al: Diurnal variation of sodium and water metabolism among patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome). Biol Psychiatry 1987; 22:224-227
- 28. Vieweg WVR, David JJ, Glick JL, et al: Polyuria among patients with psychosis: determinations and findings. Schizophr Bull 1986; 12:739-743
- 29. Vieweg WVR, Rowe WT, David JJ, et al: Self-induced water intoxication and psychosis (SIWIP): subcategory of the syndrome of inappropriate antidiuresis (SIAD). Psychiatr Med (in
- 30. Vieweg WVR, David JJ, Rowe WT, et al: Hypocalcemia: an additional complication of the syndrome of self-induced water intoxication and psychosis. Psychiatr Med (in press)
- 31. Vieweg WVR, David JJ, Rowe WT, et al. Correlation of parameters of urinary excretion with serum osmolality among patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome). Psychiatr Med (in press)
- 32. Vieweg WVR, David JJ, Rowe WT, et al: Nomograms of polyuria for men and women with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome). Psychiatr Med
- 33. White MG, Fetner CD: Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with lithium carbonate. N Engl J Med 1975; 292:390-392
- 34. Forrest JN Jr, Cox M, Hong C, et al: Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 1978; 298:173-177
- 35. Cereghino JJ: Serum carbamazepine concentration and clinical control: complex partial seizures and their treatment, in Advances in Neurology, vol 2. Edited by Penry JK, Daly DD. New York, Raven Press, 1975
- 36. Uhde TW, Post RM: Effects of carbamazepine on serum electrolytes: clinical and theoretical implications. J Clin Psychopharmacol 1983; 3:103-106
- 37. Lahr MB: Hyponatremia during carbamazepine therapy. Clin Pharmacol Ther 1985; 37:693-696

  38. Meinders AE, Cejka V, Robertson GL: The antidiuretic action
- of carbamazepine in man. Clin Sci Molec Med 1974; 47:289-
- 39. Kimura T, Matsui K, Sato T, et al: Mechanism of carbamazepine (Tegretol)-induced antidiuresis: evidence for release of antidiuretic hormone and impaired excretion of a water load. J Clin Endocrinol Metab 1974; 38:356-362
- 40. Stephens WP, Coe JY, Baylis PH: Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. Br Med J 1978; 1:1445-1447
- 41. Thomas TH, Ball SG, Wales JK, et al: Effect of carbamazepine on plasma and urine arginine-vasopressin. Clin Sci Molec Med 1978; 54:419-424
- 42. Gold PW, Robertson GL, Ballenger JC, et al: Carbamazepine diminishes the sensitivity of the plasma arginine vasopressin response to osmotic stimulation. J Clin Endocrinol Metab 1983; 57:952-957
- 43. Sordillo P, Sagransky DM, Mercado RM, et al: Carbamazepineinduced syndrome of inappropriate antidiuretic hormone secretion: reversal by concomitant phenytoin therapy. Arch Intern Med 1978; 138:299-301
- 44. Perucca E, Richens A: Water intoxication produced by carbamazepine and its reversal by phenytoin. Br J Clin Pharmacol 1980; 9:302p-304p
- 45. Perucca E, Richens A: Reversal by phenytoin of carbamazepineinduced water intoxication: a pharmacokinetic interaction. J Neurol Neurosurg Psychiatry 1980; 43:540-545
- Ghose K: Effect of carbamazepine in polyuria associated with lithium therapy. Pharmakopsychiatr Neuropsychopharmakol 1978; 11:241-245
- 47. Shukla S, Godwin CD, Long LEB, et al: Lithium-carbamazepine

- neurotoxicity and risk factors. Am J Psychiatry 1984; 141: 1604-1606
- 48. Raskind MA, Courtney N, Backus FI, et al: Antipsychotic drugs and plasma vasopressin in normals and acute schizophrenic
- patients. Biol Psychiatry (in press)
- 49. Lipinski JF, Pope HG Jr: Possible synergistic action between carbamazepine and lithium carbonate in the treatment of three acutely manic patients. Am J Psychiatry 1982; 139:948–949

#### Final Phase of Professional Activities Survey

The APA Office of Manpower Research will distribute the final phase of the Professional Activities Survey (more familiarly known as the "Biographical Directory Survey") late this summer. Over 40,000 APA members and nonmember psychiatrists will be surveyed. This follows phase I of the project, which surveyed approximately 6,000 members in the spring.

The survey serves three goals. First, it allows APA member psychiatrists to supply the basic data needed to create/update their listings for the upcoming *Biographical Directory*. Second, it enables all responding psychiatrists to indicate their recent professional accomplishments and areas of special interest and ability. This set of professional activities data will appear in the directory with the basic data, adding to the directory's value as a resource for locating colleagues, referring patients, and arranging consultations. Third, the survey collects a limited set of research data that will enhance understanding of psychiatric services and provide a quantitative basis for influencing public policy.

When the survey is received from the APA Office of Manpower Research, it should be completed and returned promptly. Completing the questionnaire will not only ensure the accuracy of the listing in the *Biographical Directory* but will also contribute to the assessment of recent developments in psychiatry. APA's Professional Activities Survey fills important needs of the membership and others in the mental health community. Survey recipients who have questions or need assistance in completing the survey should write to the APA Manpower Research Office, 1400 K St., N.W., Washington, DC 20005, or call 202-682-6216.

# Difference in Reaction Time Between Subjects With Schizotypal and Borderline Personality Disorders

Karen Chapin, Ph.D., Lois Wightman, Ph.D., Helene Lycaki, Ph.D., Norma Josef, M.D., and Gerald Rosenbaum, Ph.D.

Patients with schizophrenic spectrum disorders and affective disorders were compared on a reaction time procedure. The nonhospitalized schizotypal subjects performed similarly to the schizophrenic patients on the crossover measure. Mean reaction time discriminated between hospitalized and nonhospitalized patients rather than between types of pathology.

(Am J Psychiatry 1987; 144:948–950)

A variety of uses for the term "borderline" have been found historically in the psychiatric literature (1). "Broadly defined" (2) definitions of borderline cover a wide variety of concepts that could include borderline schizophrenia or borderline personality disorder. Spitzer and his colleagues (3) renamed and redefined the two concepts, using "schizotypal personality" to represent borderline schizophrenia and "borderline personality" to represent a more generalized unstable personality.

Recent literature has focused on the relationship between the schizotypal personality and schizophrenic disorders. Siever (4) reviewed studies that explored this relationship by using biological and psychophysiological measures. He suggested that these studies indicated that some individuals diagnosed as having schizotypal personality disorder share "common psychobiological abnormalities" with individuals diagnosed as schizophrenic. On the other hand, many studies have attempted to relate the "strictly defined borderline personality disorders" (2) to affective disorders.

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Perhaps the most stable experimental finding in the literature on the psychopathology of schizophrenia has been the consistent demonstration of deficits in attention on reaction time tasks (5). The initial study by Huston et al. (6) demonstrated greater reaction time slowing, more intrasubject variability, and earlier "crossover" (i.e., inability to benefit from regular preparatory intervals longer than 2 seconds, in comparison to irregularly presented stimuli) in schizophrenic patients. It was demonstrated that normal subjects also displayed crossover when the preparatory intervals were extended to 25 seconds. Another measure used in computing reaction time is mean latency of responding. Although it does not differentiate schizophrenic subjects from other psychiatric groups (7), it does seem to differentiate psychiatric groups from normal subjects. In other words, mean latency of reaction seems to be able to differentiate individuals who display pathology from those who do not.

This reaction time procedure has been used most often to show attentional deficit in schizophrenia. In one study (8), subjects rated as "schizotypic" were evaluated on a reaction time task and compared to normal control subjects. The authors found that the subjects rated as schizotypic showed early crossover. These subjects, however, were college students and not identified patients.

The present study was designed to replicate the classical reaction time procedure and to compare reaction time measures of attention deficits in schizophrenic subjects with those shown by patients with schizotypal personality disorder, borderline personality disorder, and major affective disorder and by normal subjects. It was hypothesized that although the subjects with schizotypal personality disorder were not hospitalized, they would show a deficit in reaction time similar to that of schizophrenic subjects. In addition, since subjects with borderline personality disorder are

seen as similar to subjects with major affective disorders, it was hypothesized that they would not show this deficit.

#### **METHOD**

Patients were recruited for voluntary participation from several psychiatry and psychology units. Subjects with schizotypal personality disorder (N=12) were selected from the outpatient departments of these units; subjects from the remaining three pathology groups were selected from hospitalized patients. The subjects were identified by the diagnosis given to them by the treatment facility. After identification, each subject was interviewed separately by an experienced psychiatrist or psychologist to decide whether the subject met all of the inclusion criteria for the diagnostic group. If these evaluations were not in agreement, the individual was not included in the study. The three groups of subjects were those with schizophrenia, undifferentiated type (N=12), those with major affective disorder (major depression) (N=12), and those with borderline personality disorder (N=12). The patients with borderline personality disorder did not have a DSM-III axis I diagnosis of major affective disorder, and the subjects with major affective disorder did not have an axis II diagnosis of borderline personality disorder. These hospitalized patients were matched as closely as possible to the schizotypal group on demographic variables. Normal subjects (N=12) were also matched on demographic variables to the patient samples. There were no significant differences between the groups on these demographic variables. The mean ±SD ages of the groups were: schizophrenia, 26.58±5.42 years; schizotypal personality disorder,  $33.25\pm10.49$  years; affective disorder,  $34.33\pm7.32$ years; borderline personality disorder, 30.92±8.72 years; and control, 28.50±6.47 years. Three groups contained eight men and four women; two groups contained seven men and five women.

The following inclusion criteria were used in the selection of all subjects for the study: 1) ability to comprehend and willingness to sign the statement of informed consent and 2) meeting the Research Diagnostic Criteria (RDC) (9) and/or DSM-III criteria for classification as schizophrenic, chronic undifferentiated type; major affective disorder, major depressive type; schizotypal personality disorder; or borderline personality disorder. Exclusion criteria for all subjects included history of brain damage or extensive ECT, substantial drug or alcohol abuse, and major medical illness. Normal potential subjects were excluded if they had an individual or family history of psychiatric problems.

After each potential subject was evaluated according to inclusion and exclusion criteria, the chosen subjects were asked to read and complete the informed consent form. Subjects were then tested using the Rodnick and Shakow reaction time procedure (10). This procedure

TABLE 1. Point of Crossover and Mean Latency for Five Groups of Subjects Given a Reaction Time Test

	Point Crossove		Latency (msec)		
Group	Mean	SD	Mean	SD	
Schizophrenic inpatients Subjects with schizotypal	7.34 <sup>b</sup>	6.34	424	170	
personality disorder Borderline personality	10.85 <sup>b</sup>	8.74	298°	55	
disorder inpatients Major affective	18.99	7.01	420	188	
disorder inpatients	18.54	9.64	370	155	
Normal control subjects	24.00	2.93	267 <sup>c</sup>	54	

a"Crossover" is a measure of ability to benefit from preparatory intervals of different lengths.

<sup>b</sup>Significantly different from borderline, affective, and normal subjects (F=9.16, df=4, 55, p=.001).

Significantly different from schizophrenic, affective, and borderline subjects (F=6.14, df=4, 55, p=.02).

tests simple reaction time to a visual stimulus (a light) at preparatory intervals of 1, 2, 4, 7.5, 15, and 25 seconds in both a regular and an irregular series.

#### **RESULTS**

Individual crossover scores and latency scores were obtained for each subject. Univariate F tests were used to examine group differences, and tests for both variables were significant. To examine group differences, post hoc analyses were performed by means of the Scheffé technique. These findings are presented in table 1.

Table 1 shows that the schizophrenic and schizotypal subjects had a similar crossover deficit, while the other three groups were not significantly different from each other on this measure. On the other hand, it can be seen that the mean latency of each group more closely corresponded with hospitalization. The schizophrenic, affective, and borderline inpatients all showed a longer latency, while the nonhospitalized subjects and normal control subjects did not.

#### DISCUSSION

These results support those of previous studies that have identified an underlying difference between patients with schizotypal and borderline disorders. It supports the position that these are two entities with separate sets of diagnostic criteria. On the reaction time measure, the schizotypal subjects displayed the early crossover that is typically found in schizophrenic subjects. In this study an early crossover was observed in both the schizophrenic subjects and the schizotypal subjects, although the schizotypal subjects were outpatients and the schizophrenic subjects were inpatients. In addition, this early crossover was not observed in the hospitalized borderline personality

disorder patients or the hospitalized major affective disorder patients.

On the other hand, the mean latencies of these groups were found to correspond to the severity of the disorder. The hospitalized subjects displayed a longer latency than the nonhospitalized schizotypal and normal subjects. This is remarkable because these schizotypal subjects concomitantly displayed an early crossover.

These findings support the differentiation of schizotypal personality disorder from borderline personality disorder. In addition, they suggest that schizotypal disorder is part of the "schizophrenia spectrum disorders," while borderline personality disorder is not.

- 1. Stone MH: The Borderline Syndrome: Constitution, Coping and Character. New York, Jason Aronson, 1978

  2. Gunderson JG, Elliott GR: The interface between borderline
- personality disorder and affective disorder. Am J Psychiatry

- 1985; 142:277-288
- 3. Spitzer RL, Endicott J, Gibbon M: Crossing the border into borderline personality and borderline schizophrenia: the development of criteria. Arch Gen Psychiatry 1979; 36:17-24
- 4. Siever LJ: Biological markers in schizotypal personality disorder. Schizophr Bull 1985; 11:564-574
- 5. Nuechterlein KH: Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. Schizophr Bull 1977; 3:373-428
- 6. Huston P, Shakow D, Riggs L: Studies of motor function in schizophrenia, II: reaction time. J Gen Psychol 1937; 16:39-82
- 7. Cromwell RL, Spaulding W: How schizophrenics handle information, in Phenomenology and Treatment of Schizophrenia. Edited by Raun WE, Karacan D, Pokorny AD, et al. New York, Spectrum, 1978
- 8. Simons RF, MacMillan FW, Ireland FB: Reaction time crossover in preselected schizotypic subjects. J Abnorm Psychol 1982; 91:414-419
- 9. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1979
- 10. Rodnick EH, Shakow D: Set in the schizophrenic as measured by a composite reaction time index. Am J Psychiatry 1940; 97:

# Phenomenology and Family History of Affective Disorder in Cushing's Disease

James I. Hudson, M.D., Margo S. Hudson, M.D., George T. Griffing, M.D., James C. Melby, M.D., and Harrison G. Pope, Jr., M.D.

Of 16 patients with Cushing's disease, 13 (81%) had lifetime diagnoses of major affective disorder according to DSM-III criteria. However, the rate of familial major affective disorder among these patients was significantly lower than that found among patients with major depression.

(Am J Psychiatry 1987; 144:951-953)

Patients with Cushing's disease (pituitary-dependent hypercortisolism) commonly exhibit affective syndromes (1–4), and conversely, patients with major affective disorder frequently display hypercortisolism (4, 5). However, the nature of the association between Cushing's disease and major affective disorder is unclear. First, what proportion of patients with Cushing's disease display affective symptoms meeting diagnostic criteria for major affective disorder? Two studies (2, 3) using operational criteria have suggested that many patients with Cushing's disease do display major affective disorder, but to our knowledge, no study has employed DSM-III criteria.

Second, if many patients with Cushing's disease exhibit major affective disorder, is this finding merely due to the effects of hypercortisolism, as suggested by the observations that nonpituitary-dependent Cushing's syndrome (1, 3, 4) and exogenous corticosteroids (4, 6) are commonly associated with affective symptoms? Or might Cushing's disease and major affective disorder be caused by a common suprapituitary abnormality that results in chronic hypersecretion of corti-

cotropin-releasing hormone (CRH)? In support of the latter hypothesis, 1) CRH-producing tumors can cause adrenocorticotropin-producing pituitary adenomas (7), 2) pituitary surgery is not always curative in Cushing's disease (8), and 3) neurohormonal disturbances, sleep abnormalities, and drug response consistent with CNS dysfunction have been reported in patients with Cushing's disease (8). However, against this hypothesis, 1) pituitary surgery is often curative in Cushing's disease (8), and 2) the responses to CRH in patients with Cushing's disease are different from the responses of patients with major depression and are most consistent with a primary pituitary lesion (5). In any event, if Cushing's disease and major affective disorder were caused by the same abnormality, one might expect high rates of major affective disorder in the relatives of patients with Cushing's disease; to our knowledge, this possibility has not yet been formally

To address these questions, we evaluated 16 patients with Cushing's disease for personal and family history of major affective disorder and other psychiatric disorders.

#### METHOD

The subjects were 16 consecutive patients (three men, 13 women; mean±SD age=44.4±14.1 years) with Cushing's disease; all had pituitary adenomas documented by CAT scan or histology and were evaluated at the Section of Endocrinology and Metabolism at University Hospital in Boston. All but one of these patients had received treatment before this evaluation.

The subjects received a semistructured diagnostic interview to determine lifetime history of the following disorders according to *DSM-III* criteria: bipolar disorder, major depression, panic disorder, agoraphobia, obsessive-compulsive disorder, substance use disorders, eating disorders, schizophrenia, and antisocial personality disorder. Information on the subjects' first-degree relatives was obtained from the probands; ill relatives were diagnosed according to *DSM-III* criteria. Morbid risk for major affective disorder was calculated as described previously (9).

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TABLE 1. Lifetime Rates of Psychiatric Disorders in Patients With Cushing's Disease and Patients With Rheumatoid Arthritis

	Cushing's Disease (N=16)		Rheumatoid Arthritis (N=14)	
DSM-III Diagnosis	Ņ	%	N	%
Major affective disorders	13	81ª	2	14
Bipolar disorder	5 <sup>b</sup>	31 <sup>c</sup>	0	0
Major depression	9 <sup>d</sup>	56	2 <sup>b</sup>	14
Anxiety disorders	3	18	0	0
Panic disorder and/or agoraphobia	1	6	0	0
Obsessive-compulsive disorder	2	12	0	0
Substance use disorders	1	6	1	7
Eating disorders (anorexia nervosa				
and bulimia)	0	0	0	0
Schizophrenia	0	0	0	0
Antisocial personality disorder	0	0	0	0

<sup>&</sup>lt;sup>a</sup>Significantly higher than rate for patients with rheumatoid arthritis (p<.001, Fisher's exact test).

blincludes one patient with psychotic features.

As a comparison group, we evaluated 14 patients (four men, 10 women; mean ±SD age=49.1±14.6 years) with rheumatoid arthritis. Personal history of psychiatric disorders according to DSM-III criteria was determined with the NIMH Diagnostic Interview Schedule (10), and family history of psychiatric disorders was assessed as just described. An additional comparison group for the family history assessment consisted of 24 outpatients with major depression. Further details of both comparison groups are described elsewhere (9).

Differences in proportions were assessed with Fisher's exact test, two-tailed.

#### **RESULTS**

The patients with Cushing's disease had an 81% lifetime prevalence rate of major affective disorder (table 1), significantly greater than the 14% rate among the patients with rheumatoid arthritis (p< .001). Among the patients with Cushing's disease with lifetime diagnoses of major affective disorder, the onset of major affective disorder preceded the onset of the medical signs and symptoms of Cushing's disease by at least 1 year in two (15%) patients, occurred within the same year as the medical signs and symptoms in three (23%), and followed the onset of the medical signs and symptoms by at least 1 year in eight (62%). The rates of other psychiatric disorders in both study groups were low.

The morbid risk for major affective disorder among the 114 first-degree relatives of the patients with Cushing's disease was 9.7%, not significantly different from the 4.8% morbid risk found in the 94 first-degree relatives of the patients with rheumatoid arthritis but significantly lower than the 23.9% morbid risk in the 108 first-degree relatives of the patients with major depression (p=.03). The lifetime prevalence rates of other psychiatric disorders among the relatives of the patients with Cushing's disease were modest and not significantly different from those found among the relatives of the patients with rheumatoid arthritis or major depression.

#### **DISCUSSION**

We found a high lifetime rate of DSM-III major affective disorder among patients with Cushing's disease—a finding comparable to that of both previous studies (2, 3) that used operational diagnostic criteria (although not DSM-III criteria). Furthermore, the rate of major affective disorder among patients with Cushing's disease was significantly higher than that found in patients with rheumatoid arthritis—a finding similar to that of Kelly et al. (2), who found a significantly higher rate of affective disorder among patients with Cushing's disease than in patients with other pituitary tumors.

By contrast, patients with Cushing's disease displayed a low rate of familial major affective disorder, similar to that found among the control group with rheumatoid arthritis but significantly lower than that found among patients with major depression. Although previous studies of Cushing's disease have not calculated the morbid risk for major affective disorder among relatives, Cohen (1) noted that six (29%) of 21 patients had family histories of depression or suicide, and Haskett (3) found that only one (3%) of 30 patients had a first-degree relative with affective disor-

The finding of only a modest familial prevalence of major affective disorder in patients with Cushing's disease argues against the hypothesis that Cushing's disease and major affective disorder are manifestations of the same suprapituitary abnormality. Furthermore, the observation that in 85% of the cases major affective disorder first appeared during or after the onset of the medical signs and symptoms of Cushing's disease supports the hypothesis that the affective disorder may be caused by hypercortisolism per se. However, the results of this study do not rule out the possibility that a subgroup of patients with Cushing's disease and major affective disorder may share a common suprapituitary abnormality.

The conclusions of this study are limited by 1) the use of semistructured, rather than fully structured, psychiatric interviews; 2) the use of the family history method, rather than the more accurate family interview method, for ascertaining psychiatric illness in relatives; 3) the use of an interviewer who was not blind to the medical diagnosis of the subjects; and 4) a small sample size. A rigorously controlled study of patients with Cushing's disease in which a larger sample were employed would be useful to confirm these findings.

Significantly higher than rate for arthritic patients (p=.04, Fisher's exact test).

dIncludes two patients with psychotic features.

#### REFERENCES

- 1. Cohen SI: Cushing's syndrome: a psychiatric study of 29 patients. Br J Psychiatry 1980; 136:120-124
- Kelly WF, Checkley SA, Bender DA: Cushing's syndrome, tryptophan and depression. Br J Psychiatry 1980; 136:125–132
- Haskett RF: Diagnostic categorization of psychiatric disturbance in Cushing's syndrome. Am J Psychiatry 1985; 142:911– 916
- 4. Kathol RG: Etiologic implications of corticosteroid changes in affective disorder. Psychiatr Med 1985; 3:135–162
- Gold PW, Loriaux DL, Roy A, et al: Responses to corticotropinreleasing hormone in the hypercortisolism of depression and Cushing's disease: pathophysiologic and diagnostic implications. N Engl J Med 1986; 314:1329–1335
- Boston Collaborative Drug Surveillance Program: Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972; 13:694

  –698
- Carey RM, Varma SK, Drake CR, et al: Ectopic secretion of corticotropin-releasing factor as a cause of Cushing's syndrome: a clinical, morphologic, and biochemical study. N Engl J Med 1984; 311:13-20
- Krieger DT: Physiopathology of Cushing's disease. Endocr Rev 1983; 4:22–43
- Hudson JI, Hudson MS, Pliner LF, et al: Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. Am J Psychiatry 1985; 142:441

  –446
- Robins LN, Helzer JE, Croughan J, et al: NIMH Diagnostic Interview Schedule, Version II. Rockville, Md, NIMH, 1980

## Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Feb. 26 and April 14, 1987.

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### Book Forum

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#### PERSONALITY DISORDERS

Essential Papers on Borderline Disorders: One Hundred Years at the Border, edited by Michael H. Stone, M.D. New York, New York University Press (Columbia University Press, distributor), 1986, 570 pp., \$55.00; \$25.00 (paper).

This is a wonderful anthology. Stone brings together 23 of the classic papers on "borderline disorders" and frames them with his own scholarly, wise, and witty overview of this extensive and complex literature. The earliest conception of borderline states can be traced to Pinel, Esquirol, and Prichard, who, in the early 1800s, described patients with severe derangements of feelings, affections, and behaviors but who did not have a corresponding impairment in their intellectual faculties. Prichard labeled this "moral insanity," and his work was furthered by Lombroso in his studies of criminality. Rosse (1890) was the first to use the term "borderline insanity" to describe those patients who were not clearly mad but also clearly not normal. The next advance was made by the great descriptive psychiatrists (Kraepelin, Bleuler, Kretschmer, and others), who developed the powerful notion of spectrum disorders. For them, borderline disorder represented a less classic expression of the same pathological processes that in their more florid form were responsible for the full-blown symptoms of schizophrenic and affective disorders. The other major contribution to the borderline literature has come in the last 50 years from psychoanalytic writers more interested in describing the border with "normal neurosis" than the border with psychosis. Analysts attempted to explain why certain seemingly good candidates for treatment do so poorly once engaged in it. In the process, the study of borderline patients has stimulated and has been stimulated by the development of psychoanalytic object relations theory and early infant observations.

What do we learn from rereading history? I think the major lesson is humility. Some of the best papers were written early, and much has been repeatedly rediscovered and rehashed (this may, of course, be true of almost everything). One does not detect a great and steady march forward toward clearer understanding and increased effectiveness in diagnosis and treatment. A second lesson is that the borderline syndromes constitute a fairly vague heterogeneity and are not likely to lend themselves to any unitary approach. The DSM-III provision of a multiaxial system and the separation of the schizotypal and borderline personality disorders may increase specificity, but much needs to be done to determine comorbidity and pathogenesis. A third lesson is that borderline personality disorder appears to have had a wide historical, geographic, and conceptual distribution and therefore is probably not, as is sometimes claimed, a local product of American psychiatry or a recent result of the decline and fall of the modern family. Perhaps the tentative ICD-10 decision to exclude a category for borderline personality deserves reconsideration.

This book will be of great value even for those who

already know most or all of the papers (a chronological run-through does wonders for one's perspective) and will also serve as an excellent introduction for those who are not familiar with the field and want to place the currently burgeoning literature in context. One might argue here and there with the selection of some of the papers (i.e., there is perhaps an overemphasis on psychoanalytic contributions and not enough on the descriptive, somatic, and cognitive approaches), but Stone generally summarizes very well what he does not include and no selection would satisfy everyone. For me, the special gem of the collection (and, from now on, required reading for my trainees) is the 1947 paper on treatment by Melitta Schmideberg.

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Unmasking the Psychopath: Antisocial Personality and Related Syndromes, edited by William H. Reid, Darwin Dorr, John I. Walker, and Jack W. Bonner III. New York, W.W. Norton & Co., 1986, 300 pp., \$34.95.

If I were interested in obtaining a useful book on antisocial personality, I would look for one offering a historical overview and a discussion of diagnosis and differential diagnosis, clinical findings, natural history and outcome, complications, epidemiology, etiology, and both somatic and psychosocial treatments. Unfortunately, this book, which was based on a conference organized as a joint project of Highland Hospital and Duke University, does not provide these. Because of the many omissions, I cannot recommend the book.

What the book does provide is an assortment of loosely connected chapters having to do with sociopathy and related disorders. The book begins with a chapter by Robert Hare in which he relates his years of experience researching sociopathy, outlining apparent physiological differences between the sociopath and others. Although portions of the chapter are interesting, it would have been more valuable had he written a more general historical overview of sociopathy and highlighted definition and diagnosis. A chapter by Remi Cadoret on the epidemiology of antisocial personality, relying in large part on his own extensive research, provides the most sound, data-based chapter in the book. Gerald Brown and Frederick Goodwin of the National Institute of Mental Health (NIMH) provide an interesting chapter on human aggression from a biological perspective. They correlate both violence and suicide with low CSF 5-hydroxyindoleacetic acid (5-HIAA). Their data are not specific to antisocial personality and, while intriguing, do not seem to fit in with the rest of the book. William Barley provides an excellent summary of behavioral and cognitive treatments that have been tried in sociopaths and delinquents. He observes that some of these interventions "offer promise for problems of juvenile delinquency and antisocial personality disorder, but their research base with these persons is limited. Behavioral interventions clearly produce short-term change, but there is much less evidence that they produce long-term alteration of behavior." His observation highlights the problem with most of these treatments. They may be effective in altering behavior while patients are institutionalized, but the improvement does not generalize. Larry Strasburger writes of his experience treating antisocial patients with individual, psychodynamically oriented psychotherapy. His chapter is filled with practical advice and guidelines on handling countertransference, but his wisdom would seem to apply to most patients, not just those who are antisocial. Several chapters are devoted to inpatient treatment, including treatment of the antisocial young person and an exploration of the therapeutic milieu believed helpful for treating these persons. The various authors base much of their writings on their own experience with antisocial patients, but the chapters are devoid of objective research findings. This is the tragedy of most work on the treatment of antisocial individuals. Everyone has strongly held opinions about what should be done, everyone has a belief that something must be done, but no one has any data to demonstrate that what they do is beneficial.

I liked several chapters in the book a great deal, including those by Cadoret, Barley, Brown and Goodwin, and even the one by Strasburger. Unfortunately, because the book lacks chapters on history, diagnosis and differential diagnosis, clinical findings, natural history and outcome, complications, etiology, and somatic treatments, the book is incomplete and may give the uninitiated reader an inaccurate picture about sociopathy. For those who are knowledgeable about sociopathy, the book may contain some useful insights.

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#### **SCHIZOPHRENIA**

Schizophrenia: An Integrative View, edited by C.L. Cazzullo and G. Invernizzi. London, John Libbey, 1985, 402 pp., \$38.00.

This volume represents the proceedings of an international meeting on schizophrenia held in Milan, Italy, in June 1984. The book resembles a historian's account of the Roman Empire. It covers a very large amount of territory, is made up of contributions from several continents, contains a collection of diverse subjects, and has a decided overall Mediterranean influence. This latter is so because more than half of the 42 chapters in the book are from Italian contributors; the University of Milan is the source for the majority.

The book is divided into four sections: Cultural and Social Aspects, The Psychic Milieu, Biological Aspects, and Integrative Strategies for Treatment. In turn, each of these four sections contains between seven and 15 chapters. I found this book uneven in quality: several well-written and thoughtful summaries of topic areas and presentations of experimental data contrast with fuzzy, rambling contributions. Chapters vary in length; some are only two or three pages long but in-depth reviews go up to 30 pages. Some of the chapters deserve specific mention, and I will outline these here.

In order of presentation, some of the more notable contributions are Balestrieri's argument for a transdisciplinary view of schizophrenia that would include basic and clinical sciences, a brief but thoughtful contribution from Hamilton

on (among other topics) the relevance of hallucinations and delusions to the veridical nature of our knowledge of the external world, and a chapter by Andreasen that contains a clearly written argument for defining, quantifying, and classifying schizophrenia through casting a broad but reliable defining net. Users of the Montgomery-Asberg Depression Rating Scale will be interested to see a chapter by Montgomery's group on the development of a similar Schizophrenia Rating Scale that is also sensitive to change. Hanbauer, Memo, and Kleinman present preliminary data on dopamine in schizophrenia, specifically D1 receptor coupling with adenylate cyclase.

Ivanyi and Droes present an excellent review of human lymphocyte antigen (HLA) histocompatability antigens in schizophrenia that complements the subsequent overview by Nurnberger et al. on the genetics of schizophrenia. Cazzullo et al. present an interesting study on cerebral ventricular size in schizophrenic and schizophreniform patients as well as data on the seasonal nature of birth of schizophrenic patients in the Italian population. Shagass et al. present an excellent review of brain electrical potential research in schizophrenia, and Maj and Kemali discuss schizoaffective disorder. Other chapters of interest include van Kammen and Gelernter on norepinephrine studies in schizophrenia and Bunney et al. on new psychopharmacological treatments. Reda discusses historical perspectives on early therapies for mental illness, and Seeman and Hauser discuss the relationship between gender and schizophrenia.

The book lacks a strong editorial voice. As with other books of this type, where diversity is a strong theme, an editorial contribution in the form of one or more summaries or a careful introduction can help to organize and tie the material together. One misses this. Stronger editorial intervention would have also helped in pointing out links between chapters where themes obviously overlap. One such example occurs in chapters by Cazzullo and by Seeman and Hauser that discuss, respectively, gender-related symptomatic differences in schizophrenia at initial presentation and dopamine receptors and gender in schizophrenia.

There are problems with the publishing end of the book. The version that I received has a serious printing error which omitted four chapters (numbers 7 through 10, by Borgna, Paldolfini and Ciani, Sartorius, and Denber) by deleting pages 55 through 86 and repeating pages 23 through 54 in their place. Many of the chapters of Italian origin are burdened by problems of translation and proofreading that conspire together to produce real difficulties with smooth reading of the text as well as unintentionally amusing passages. A typical example comes from one chapter: "The prognosis of this form of schizophrenia is deeply correlated to non-pharmacological phase of intervention, aimed at reducing symptomatologically the clinical picture, it is necessary to work on the intrapsychic familial and social milieu" (p. 8). When problems of this type are frequent, as they are in this book, the extraction of the author's intended meaning is frustrating and time-consuming and the overall quality of the book suffers. Remnants of the original meeting format also need editing out. On page 348, "Dr. Sarwer Foner, one of 3 main speakers" is invited in one paper to deliver next a lecture on integrative strategies for treatment, which is not included in the volume at all. Some basic proofreading by a reader-friendly publisher would have helped with all of the above problems.

A suggested approach for the reader is to regard this collection as one might an extra large psychiatry journal or a multi-author short story omnibus. Sample everything that

looks appealing, finish everything worthwhile, and reread everything that deserves it. There are enough worthwhile contributions here to engage any reader with an interest in schizophrenia. This is certainly a book to borrow, maybe a book to buy.

GODFREY D. PEARLSON, M.D. Baltimore, Md.

Recovery From Schizophrenia: Psychiatry and Political Economy, by Richard Warner. New York, Methuen, 1986, 380 pp., \$37.95.

This volume provides a breath of fresh air for the current literature on schizophrenia. It is a book about schizophrenia as a social-contextual problem—not as a disease. Warner does not ease the reader into his unfashionable view of this disorder. The introduction's opening paragraph asks three questions:

Does the way we make our living or the form of government under which we live affect whether or not we become insane? Does social class or the state of the economy influence whether schizophrenics recover from their illness? Has industrial development affected the number of schizophrenics who become permanently and severely disabled—lost to their families, costly to the community and leading lives of emptiness and degradation?

Carefully read, the second paragraph of the introduction will likely shock, surprise, or amaze some of our colleagues and will be disbelieved by many clinicians trained since 1970 or so. Warner challenges three myths prevalent in today's majority thinking about schizophrenia when he says 1) that the neuroleptics have not improved the long-term outcome of schizophrenia, 2) that the neuroleptics are not the principal reason the large mental hospitals have been emptied, and 3) that the outcome of schizophrenia is not similar in all cultures. Although not included in that introductory paragraph, yet another mythological balloon is subsequently pricked: Warner states that the long-term outcome of schizophrenia is not necessarily poor.

Unrelenting, after a page outlining his materialist theoretical approach and another describing chapter contents, he states his major thesis in the first sentence of the first chapter: "Schizophrenia is an illness that is shaped, to a large extent, by political economy."

Warner does not go so far, however, as to take a radical Marxist stance. That is, he does not espouse the position that economic factors, in particular the exploitative capitalist industrial revolution, with its need for a labor surplus, cause chronic disabling psychosis. He confines his argument to the influence of economic factors on the prevalence, course, and outcome of psychosis. In some ways it is disappointing that he does not describe the more radical materialist position. It is a point of view that warrants a clear and careful exposition to an American mental health audience.

Although Warner's position is not likely to be popular in today's "schizophrenia as brain disease" context, even the most critical disbelievers will have difficulty faulting his scholarship. Chapter two, "Health, Illness and the Economy," for example, reviews a vast number of studies (I stopped counting at 100) supporting the idea that there is

more illness when there is more unemployment. This is must reading for everyone involved with the homelessness issue. Psychiatry, in concert with politicians, the media, etc., has been so busy blaming deinstitutionalization for homelessness that adequate recognition has not been given to the role of unemployment in producing homelessness. The unemployment rate in the United States went from around 7% in 1979 to 11% (or more than 10 million persons) by late 1981. Warner would posit that the one-third or so of the homeless who are mentally ill are mostly persons who are manifesting the increased incidence of mental illness that results from unemployment. He would find unemployment, not deinstitutionalization, the major culprit in the production of homelessness. I can only agree (1).

My major criticism of the book is that Warner may have bitten off more than his audience can chew. Even though each chapter provides a summary, it is at times difficult to sort out the highly relevant and important from the merely interesting and supportive. For example, chapter three, "Recovery From Schizophrenia," while a scholarly tour-deforce, fails to highlight the four preneuroleptic-era long-term follow-up studies now available that give us reason to be much more optimistic than we have been about outcome in schizophrenia. These 20-plus-year follow-up studies, by Bleuler (2), Ciompi (3), Harding et al. (4), and Huber et al. (5), yielded remarkably consistent results: 60%-85% of schizophrenic patients, depending on the criteria used, had achieved good social recoveries. It is quite impressive that studies spanning an almost 50-year period (1938-1986) in three countries (West Germany, Switzerland, and the United States) found such remarkably consistent 20-year results. I would have liked these data to have been highlighted.

Part three of the book, Treatment, is also unconventional. For example, Warner summarizes a literature that supports neuroleptic drug-free treatment of newly diagnosed schizophrenic patients—if a proper treatment milieu can be provided (a very big "if" in my own experience). The last two chapters in that section, "Work" and "Desegregating Schizophrenia," show clearly where Warner's heart lies. A job is clearly the most universally legitimizing role in this society. Hence, work is central to Warner's treatment focus.

The last page of the book, like the first, is a real zinger. Warner makes seven extraordinarily sensible, data-based recommendations that, if implemented, would make it possible for most persons labeled schizophrenic to lead meaningful, productive, and satisfying lives in our society. He then asserts that their implementation would require a radical restructuring of society; I'm not sure I totally agree with him on that point. Although it is not included, as such, in his recommendations, I believe we could legislate a system of national health insurance without significant risk for the extant structure of our society. By providing reliable and predictable financing, such a system should facilitate the implementation of Warner's recommendations. Although I disagree with the "radical restructuring" Warner envisions, I must agree with the sense of what he's saying—that this society is not really ready to desegregate and re-empower schizophrenic patients to the degree that seems necessary to convert an often malignant condition (as currently dealt with) into a mostly benign one.

Although Warner's overall thesis and point of view are ones with which many will disagree, the book brings together such a diverse body of literature that it should be read by serious scholars of madness. It is especially recommended for psychiatric epidemiologists, social and cross-cultural psychiatrists, and all community mental health personnel.

#### REFERENCES

- Mosher L: Book review, Lamb HR (ed): The Homeless Mentally Ill. JAMA 1985: 254:428-429
- Bleuler M: A 23 year longitudinal study of 208 schizophrenics and impressions in regard to the nature of schizophrenia, in The Transmission of Schizophrenia. Edited by Rosenthal D, Kety SS. Oxford, Pergamon Press, 1968
- Ciompi L: Catamnestic long-term study of the course of life and aging of schizophrenics. Schizophr Bull 1980; 6:606–618
- 4. Harding CM, Brooks JW, Ashikaga T, et al: Aging and social functioning in once-chronic schizophrenic patients 21–58 years after first admission: the Vermont Study, in Schizophrenia, Paranoia and Schizophreniform Disorders in Later Life. Edited by Hudgins R, Miller R. New York, Guilford Press (in press)
- Huber G, Gross G, Schuttler R, et al: Longitudinal studies of schizophrenic patients. Schizophr Bull 1980; 6:592–605

LOREN R. MOSHER, M.D. Bethesda, Md.

Contemporary Issues in Schizophrenia, edited by Alan Kerr and Philip Snaith with the assistance of Stanley Thorley and Alison Campbell. London, Gaskell (Royal College of Psychiatrists) (Washington, D.C., American Psychiatric Press, distributor), 1986, 469 pp., \$48.00.

This is a special publication of the *British Journal of Psychiatry*, an update of the last 15 years of that journal's articles on schizophrenia for "students, researchers and clinicians." A considered offering by an august body of psychiatrists, the book has much to offer and will find its way into most psychiatric libraries. But it is not without flaws.

This is the work of 54 authors, 30 from the United Kingdom, 16 from North America, and a sprinkling from other places, including one each from Iceland and Tasmania. There are 47 chapters: 32 are condensed versions of "outstanding" papers (predominantly reviews) or groups of papers (correspondence) from the pages of the *British Journal of Psychiatry*, and 15 are especially commissioned overviews. The reprinted papers have been abbreviated by the removal of tabular data and summaries.

The chapters are assembled under seven headings: General and Historical Concepts, Classification and Phenomenology, Organic Aspects, Genetic Aspects, Social Aspects, Treatment, and Outcome. The section on organic aspects is disappointing, with extensive mention of seasonality, the viral hypothesis, and the positive versus negative symptoms debate. There is almost nothing of what is called biological psychiatry in other quarters. My choice would have been to include Reveley's 1985 paper (1) here and leave out one of his two commissioned papers from other sections of the book. The other sections are all strong.

Highlights of this volume are difficult to decide on because the standard is consistently high. Since most psychiatrists are already familiar with the reprinted works, it is the recently commissioned articles that attract particular attention. These include "The Classification and Phenomenology of Schizophrenia" by R.E. Kendell, "Temporal Disorientation in Chronic Schizophrenia" by T.J. Crow, "Assessment of Familial Risks in Schizophrenia and Their Application in Genetic Counselling" by D.W.K. Kay, "Recent Research on Relatives' Expressed Emotion" by Julian Leff, "Rehabilitation" by Robin G. McCreadie, and "Depressive Symptoms in Schizophrenia" by D.A.W. Johnson.

It is probably impossible to compile a book that will suit students, researchers, and clinicians. Because this is a collection of reviews, repetition of information becomes a problem. The abbreviation of outstanding papers results in something that is less than outstanding. Before using the information contained one feels the need to return to check the original. The removal of most tabular data makes the reading heavy going. A teacher would not be able to take many useful slides from these pages.

This book has two parts—a ready reference system to some of the excellent papers that have appeared in the *British Journal of Psychiatry* over the last 15 years and a collection of previously unpublished overviews. It is a monument to British psychiatry and will be of greatest value to those studying for postregistration specialist qualifications.

#### REFERENCE

 Reveley MA: Ventricular enlargement in schizophrenia. Br J Psychiatry 1985; 147:233–240

SAXBY A. PRIDMORE, M.B., B.S. Hobart, Tas., Australia

#### DYSKINESIA

Dyskinesia: Research and Treatment, edited by D.E. Casey, T.N. Chase, A.V. Christensen, and J. Gerlach. New York, Springer-Verlag, 1985, 230 pp., \$34.50.

The title of this book seems to promise a comprehensive review of the range of dyskinesias, but its true focus can be judged by the cover, which boasts a series of photographs of an elderly woman with severe orofacial dyskinesia. The contents are limited, almost exclusively, to the topic of drug-induced tardive dyskinesia.

This relatively slim volume represents the proceedings of an international symposium and comprises 27 papers by 64 authors, virtually all of whom are recognized authorities in the areas they discuss here. Energetic editing has produced a consistency of style and appearance in the collected contributions and generated a helpful list of contents and an abstract at the beginning of each paper as well as useful cross-referencing between the papers.

The book has been divided into three sections. The first, entitled Preclinical Aspects, consists mainly of papers concerned with the interpretation of dopamine receptor binding studies. The various neuropharmacological hypotheses propounded refer to a possible functional distinction between different dopamine receptors. The article by Scheel-Krüger and Arnt presents an intriguing pathophysiological theory for tardive dyskinesia. Their main hypothesis is that the condition reflects a disturbed balance between distinct dopaminergic neuronal systems in the brain. In the next section, Clinical Aspects, Gerlach argues, similarly, that the manifestation of tardive dyskinesia may depend on a subtle balance between various neurotransmitters and the sensitivity of subtypes of dopamine receptor in different brain regions.

Stahl (1) recently referred to the "quiet revolution" in contemporary thinking about tardive dyskinesia, citing the careful elucidation of the epidemiology and natural history of the condition and its relationship to psychiatric diagnosis. He considered such work a requisite for serious research into the treatment and prevention of tardive dyskinesia. The potential of such an approach is hinted at in some of the papers in the Clinical Aspects section, particularly those by

Kane et al., Owens, and Casey. Their three papers address, respectively, the risk factors for tardive dyskinesia, the relationship between tardive dyskinesia and the involuntary movements associated with schizophrenia, and the long-term outcome of the condition when the dose of antipsychotic drugs is decreased or the drugs are withdrawn. However, these papers, along with most of the contributions in this book, are disappointingly brief and sketchy, containing little speculation on the implications of the findings described.

The few papers on treatment for tardive dyskinesia cover a wide range of drugs that have been tested, many of which have only the most tenuous rationales for possible antidyskinetic properties. There is little here to encourage optimism about the search for a safe and effective treatment. In his second chapter in this section, Casey concludes that "for the majority of patients, it may be best to give no drug treatment" (p. 141).

The last section concerns Animal Models. The hope remains that these will play a valuable role in the testing and development of new antipsychotic agents without the side effects of tardive dyskinesia and other motor disorders. However, assessing the potential of a drug for inducing motor side effects in man on the basis of rat studies involves a dubious extrapolation from the effects of chronic dopamine antagonists on neurotransmitter levels and dopamine receptor binding characteristics in the rodent brain and behavioral responses to the administration of dopamine antagonists. In monkeys receiving long-term administration of antipsychotic drugs, a motor syndrome can be produced that at least resembles tardive dyskinesia in man. However, as Domino points out, research in subhuman primates has practical restrictions, such as high cost, long duration, and the limited availability of suitable animals.

In summary, a variety of interesting neuropharmacological theories are presented in this book, but all remain unsubstantiated. No promising treatments or new management strategies for tardive dyskinesia emerge. However, some of the reports of clinical investigations yield heuristic data on the nature of the condition, predisposing factors, and treatment variables.

This is not a book for the general psychiatrist, but perusal is recommended for researchers in the field of drug-induced movement disorder who are seeking inspiration; the clues are probably here.

#### REFERENCE

 Stahl SM: Tardive dyskinesia: natural history studies assist the pursuit of preventive therapies. Psychol Med 1986; 16:491

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#### IMPACT OF MENTAL ILLNESS ON THE FAMILY

Family Approaches to Major Psychiatric Disorders, edited by Melvin R. Lansky, M.D. Washington, D.C., American Psychiatric Press, 1985, 147 pp., \$12.00 (paper).

Working With Families of the Mentally Ill, by Kayla F. Bernheim, Ph.D., and Anthony Lehman, M.D. New York, W.W. Norton & Co., 1985, 235 pp., \$22.95.

In his introduction to Family Approaches, Dr. Lansky briefly summarizes the history of family therapy's develop-

ment and points out that it became clear years ago that family therapy cannot cure schizophrenia or other major psychiatric disorders. With that realization, family therapists turned away from the major disorders.

This volume, which is a collection of papers expanded from panel presentations at the 1984 annual meeting of APA, advocates the use of integrative family therapy in the treatment of disorders that are not caused by disturbances in interpersonal relationships—i.e., the major disorders. The rationale for family therapy is to bring together the treatment of the psychosocial pathology (the conflict) with that of the biological pathology (the deficit) because integrated treatment of both is needed and will be more effective. The integrative family therapist must have superior understanding of psychodynamics, social systems, systems theory, and the various disease entities.

Five of the six chapters illustrate the uses of family treatment in the specific disorders of alcoholism, bipolar disorder, schizophrenia, organic brain syndrome, and cancer. The other deals with the treatment of narcissistic vulnerability in marriage. Such vulnerability amounts to major psychopathology in family members in that it requires their constant defensive vigilance. Defenses against narcissistic injury may take precedence over everything else, so that the family is untreatable unless they are recognized and the pathological narcissism is treated. No one has figured out how to do that very well yet, however, so the other five chapters are written in a more practical vein. These chapters outline strategies that have been valuable in treating families without narcissistic vulnerability, at least not in its extreme form.

The essence of family therapy technique is to be a patient, knowledgeable, nonjudgmental participant and observer. These papers are variations on that theme, ranging from the use of psychodynamic and structural strategies to treat alcoholic families and psychodynamic work with families of bipolar patients to a combination of supportiveness and education with families in which a member is demented, is schizophrenic, or has terminal cancer.

Working With Families of the Mentally Ill is dedicated to such families and to the concept that schizophrenia is a disease of the brain, not one that is caused by families. John Talbott, in his foreword, sets the tone with the statement, "This book is not about doing therapy to families, it is about working with them, and as most know, there is a world of difference" (p. iv). The book is both a plea for this attitude toward the disease and the families involved and a detailed guide for the "family clinician." The treatment strategies are supportive, educational, and behavioral.

One must first recognize the plight of the family in its bewilderment as to how to treat and what to expect from the patient, while being stigmatized according to the theory of parental schizophrenigenesis. These families are generally eager for compassionate, competent help; the authors cite studies showing that the majority of them have been dissatisfied with their experience with mental health professionals. The authors believe that family therapy will do more harm than good if it is based on theories of family etiology. They recommend supportive family counseling, which recognizes that the patient's illness traumatizes the family and that family responses can make or break the patient's treatment. Supportive family counseling tries to help both the patient and the family through support, understanding, and information, including explicit advice.

This book has three sections. The first, Charting a New Course, is an exposition of the problem and a proposal in general terms. The second, Nuts and Bolts, seemed to be titled in bad taste, but I found none of that in the text. It is the how-to-do section. The last section, Professional Dilemmas, has observations and assertions about key attitudinal and conceptual issues in the mental health professions. The authors point out that if we too narrowly apply the medical model we neglect opportunities for psychosocial intervention; to view the family as the etiological agent is even worse. I was reminded of the axiom I embraced when I entered psychiatry in the late 1950s: "The parents did as well as they could do, so we ought not to think of them as pathogens, or at least not treat them as such."

That attitude was a precursor of our modern sophistication regarding neurochemistry and genetics, and it might be a reasonable middle ground between the poles of the medical and psychosocial models of pathogenesis. This book emphatically supports the exculpation of parents of psychotic individuals. The authors recommend that families join the National Alliance for the Mentally Ill, and there is an appendix that lists the addresses and phone numbers of all the chapters

WILLIAM R. FLYNN, M.D. Napa, Calif.

Family Management of Schizophrenia: A Study of Clinical, Social, Family, and Economic Benefits, edited by Ian R.H. Falloon. Baltimore, Johns Hopkins University Press, 1985, 193 pp., \$26.50.

This slim volume impressively responds to growing concern over an unresolved problem: schizophrenia remains inadequately treated with neuroleptic medication alone. The rate of florid relapses in the first year after discharge from the hospital has continued at 35% to 40% in controlled studies with either an oral neuroleptic or injectible fluphenazine decanoate. Furthermore, for patients without positive (florid) symptoms, the negative (deficit) symptoms have produced an alarming toll of social and occupational disability, distress and burden for families of deinstitutionalized patients, and high economic cost for the community.

Falloon and his colleagues have brilliantly demonstrated that treatment results can be improved through well-structured programs of "family management," which in his work means a sophisticated combination of family psychoeducation and behavioral family therapy. The research methods and findings reported in this volume have been partially published before (1–4), including an article in the *New England Journal of Medicine* (2)—a recognition seldom achieved by psychiatrists and even less by those with a psychosocial orientation. This book adds and integrates important new research data, but a companion volume (5) should be consulted for a detailed description of the clinical methods.

Current family treatment approaches to schizophrenia were stimulated by the research of Brown et al. (6) and Vaughn and Leff (7) on expressed emotion. Replicated studies showed that florid relapses of schizophrenic patients living with relatives were significantly more frequent when key family members expressed critical and/or overinvolved attitudes toward the patient. Falloon's intention was to select a sample of 36 schizophrenic patients at risk for relapse because initial assessment indicated that they were in daily contact with a high-expressed-emotion family. Unfortunately, no low-expressed-emotion comparison group was

included. Instructively, in this book Falloon himself provides the best critique to date of the limitations of the expressed emotion hypothesis. The study convincingly demonstrates that comprehensive community management can usefully focus on problem solving and communication skills of families rather than on the explicit issue of reducing family expressed emotion.

The major thrust of the Falloon project was to compare home-based family management with hospital-based individual patient care. All patients and families concomitantly received high-quality comprehensive case management, crisis support, and independently monitored drug therapy. Given a considerable overlap in the two approaches, the results were strikingly consistent across multiple forms of independent assessment in showing superior outcomes with the family approach over a 2-year period. These findings were evident not only in fewer florid symptoms and relapses and in smaller drug doses but also in fewer negative symptoms and better social adjustment. Distinctively, in this study the effects on the family unit as well as on the patient were examined. Family members experienced less distress and burden, better problem solving and family coping, and less patient-related disruption in their daily lives. An economic analysis showed that despite the added cost of conducting most family sessions in the homes, the overall cost of care was less for the family management patients. Other data analyses of biological variables, life events measures, and observed family interaction variables add to the high density of the thought-provoking information provided in this vol-

As a follow-up to this study, replications are needed and are underway. In addition, further systematic studies are needed of other patient-family samples and other viable alternatives, such as intensive social skills training of the patient (8), clinic-based family therapy, multiple family group therapy, group home and day treatment approaches, and, most crucially at present, the contributions of family self-help groups and consumer advocates. The "optimistic initial findings" of the Falloon study will indeed serve to "encourage investigators in a field of major public health significance" (p. 181).

#### REFERENCES

- Falloon IRH, Boyd JL, McGill CW, et al: Family management training in the community care of schizophrenia, in New Developments in Interventions With Families of Schizophrenics. Edited by Goldstein MJ. San Francisco, Jossey-Bass, 1981
- Falloon IRH, Boyd JL, McGill CW, et al: Family management in the prevention of exacerbation of schizophrenia: a controlled study. N Engl J Med 1982; 306:1437-1440
- Falloon IRH, Boyd JL, McGill CW, et al: Family management in the prevention of morbidity of schizophrenia: clinical outcome of a two-year longitudinal study. Arch Gen Psychiatry 1985; 42:887-896
- Falloon IRH, Pederson J: Family management in the prevention of morbidity of schizophrenia: the adjustment of the family unit. Br J Psychiatry 1985; 147:156–163
- Falloon IRH, Boyd JL, McGill CW: Family Care of Schizophrenia: A Problem-Solving Approach to the Treatment of Mental Illness. New York, Guilford Press, 1984
- Brown GW, Birley JLT, Wing JK: Influence of family life on the course of schizophrenic disorders: a replication. Br J Psychiatry 1972; 121:241–258
- Vaughn CE, Leff JP: The influence of family and social factors on the course of psychiatric illness: a comparison of schizophrenic and depressed neurotic patients. Br J Psychiatry 1976; 129: 125-137

8. Hogarty GE, Anderson CM, Reiss DJ, et al: Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia, I: one-year effects of a controlled study on relapse and expressed emotion. Arch Gen Psychiatry 1986; 43:633–642

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The Family and Schizophrenia, by John G. Howells and Wahuih R. Guirguis. New York, International Universities Press, 1985, 346 pp., \$35.00.

This book is a review of theories and research concerning the family environment as an etiological factor in the development of schizophrenia. The authors review the work of major theorists in this area (Murray Bowen, Lyman Wynne, Don Jackson, Theodore Lidz, and R.D. Laing) on a chapter-by-chapter basis. The remaining chapters deal with related studies and methodological issues. The authors are keenly aware of the methodological limitations of the studies they review, and, in this sense, the book could be of value to those becoming acquainted with this interesting area of research.

The book is not, however, a review of the current state, or even the most recent state, of research in this area. In fact, the book appears to have been written 10 or more years ago and may have been minimally updated for publication in the 1980s. This is a serious limitation of the book, since the area of family factors in schizophrenic illness has blossomed in the past decade, and many of the methodological limitations characteristic of the original studies have been addressed. There is scant reference to recent research in this field by behaviorally oriented family therapists such as Liberman, Anderson, Falloon, and Leff. Particularly neglected are studies of schizophrenia and family intervention (e.g., Goldstein et al. [1], Falloon et al. [2], and Leff et al. [3]) and the longitudinal studies of family factors and schizophrenic onset (e.g., Doane et al. [4]). Furthermore, there is little or no reference to studies of expressed emotion and the course of schizophrenia beyond a brief discussion of the original work of Vaughn and Leff (5), which has been replicated and extended considerably since its publication. Finally, the numerous studies of communication deviance, a factor that has been found to discriminate parents of schizophrenic patients from parents of nonschizophrenic patients, receive little attention beyond a discussion of the original work by Wynne and associates. This is a rather serious omission given the authors' claim that families of schizophrenic patients have not been shown to be different from families of "severe neurotics." The most current studies cited by the authors are typically their own.

The authors submit each study to a methodological critique following a discussion of the results. The summaries of the works are well detailed. The critiques, however, are extremely predictable and often pedestrian. The major thesis of the book seems to be that the original investigators were not really studying schizophrenic patients at all but, rather, patients with "severe neuroses" or "severe emotional disturbance." This claim is rarely supported by convincing arguments or case examples. For instance, the authors claim that in studies where parents of schizophrenic patients did not differ or differed only moderately from parents of patients with character disorders, the schizophrenic patients must really have had character disorders. A similar confusion is drawn about the majority of the other studies reviewed in

this book, even in cases where patients had been hospitalized chronically or intermittently for years before study (Bowen's work). It is not even clear what the authors consider a "severe neurotic" or what diagnostic criteria they used to support this claim. They make no mention of DSM-III, Research Diagnostic Criteria, or most of the other diagnostic systems currently in use.

The authors provide rigorous critiques of the various methodologies used in these studies. They do not approve of the retrospective, longitudinal, or cross-sectional methods but fail to offer alternative research strategies. Their criticisms often seem to miss the point the studies were trying to convey. For instance, they criticize Wynne's studies because the experimental and control groups were not matched on IQ, which they claim is "the most important single variable in such a study" (pp. 313–314). They occasionally buttress their arguments for alternative interpretations with "the authors' clinical experience."

It is not clear what Howells and Guirguis's own view of schizophrenic development is, although they claim that biological factors alone account for the development of "process schizophrenia," while biological and stress factors may account for "nonprocess schizophrenia which covers neurosis and is qualitatively different from true schizophrenia in its emotional root" (p. 328). They seem to avoid the notion of an interactive, diathesis-stress model. They conclude by stating that the studies they reviewed "are independent of any views on the etiology of schizophrenia" (p. 316).

This book may be of use to students who would like a historical overview of the development of the field. For the researcher who is seriously interested in the topic, however, the book does not adequately represent the current state of this field and does not discuss methodological issues that are currently of interest to investigators (e.g., how to code family interactions, how to analyze sequences of interactional behaviors, how to distinguish trait from state markers). Books such as Lansky's (6) and McFarlane's (7), which provide more sophisticated, in-depth, and less biased overviews of this area of research, may be of more use to experienced researchers.

#### REFERENCES

- Goldstein MJ, Rodnick EH, Evans JR, et al: Drug and family therapy in the aftercare of acute schizophrenia. Arch Gen Psychiatry 1978; 35:1169–1177
- Falloon IRH, Boyd JL, McGill CW, et al: Family management in the prevention of exacerbations of schizophrenia: a controlled study. N Engl J Med 1982; 306:1437-1440
- Leff J, Kuipers L, Berkowitz R, et al: A controlled trial of social intervention in the families of schizophrenic patients. Br J Psychiatry 1982; 141:121-134
- Doane JA, West KL, Goldstein, MJ, et al: Parental communication deviance and affective style: predictors of subsequent schizophrenia spectrum disorders in vulnerable adolescents. Arch Gen Psychiatry 1981; 38:679

  –685
- Vaughn CE, Leff JP: The influence of family and social factors on the course of psychiatric illness: a comparison of schizophrenic and depressed neurotic patients. Br J Psychiatry 1976; 129:125-137
- Lansky MR (ed): Family Therapy and Major Psychopathology. New York, Grune & Stratton, 1981
- McFarlane WR (ed): Family Therapy in Schizophrenia. New York, Guilford Press, 1983

DAVID J. MIKLOWITZ, PH.D. DAWN I. VELLIGAN, M.A., C.PHIL. Los Angeles, Calif. Suicide and Depression Among Adults and Young Adults, edited by Gerald L. Klerman. Washington, D.C., American Psychiatric Press, 1986, 373 pp., \$24.95.

In his remarks about suicidal behavior among young people, Gerald Klerman emphasizes the currently recognized fact that "the issue of adolescent suicide and depression has become a matter of public policy and increasing national concern" (p. 365). As editor of this book, which was based on a 1982 conference in Boston entitled Preventive Aspects of Suicide and Depression Among Adolescents and Young Adults, Dr. Klerman integrates the presentations of highly respected clinicians and researchers in the fields of clinical psychiatry, developmental psychology, epidemiology, and public health. A major theme is the search for ways to promote the mental health of today's youth. Thus, much of the book uses a public health and epidemiological approach that espouses identification of risk factors, incidence data for youth suicide, and subsequent development of prevention strategies. This focus is evident throughout the book.

The authors provide divergent views on topics related to suicidal behavior in adolescents and young adults. Many chapters are specific to issues of suicide and depression, but others offer insights about developmental, family, and social concerns that have implications for understanding suicide in the young. Throughout, research strategies and prevention techniques are suggested. These suggestions are a major strength of this book.

A number of chapters discuss theoretical and research findings regarding adolescent and young adult development. Daniel Levinson reviews a theory of life structure, and Anne Petersen and W. Edward Craighead discuss emotional and personality development in youth. In an innovative chapter, Pamela Perun and Sumru Erkut suggest that adolescent well-being "is to be understood in the context of the timing of events in individual lives, and relative to sociohistorical changes in the social construction of adolescence" (p. 258). They contend that adolescence has not remained constant but "has been both shortened and lengthened . . . in response to social and historical process of change" (p. 264). They believe that such change produces stress which can affect a particular cohort of adolescents at a particular time. These ideas enhance the scope of efforts to understand family and genetic factors associated with affective disorders so well described in chapters by Myrna Weissman on "Being Young and Female: Risk Factors for Major Depression" and by Theodore Reich et al. on "Genetic Risk Factors for the Affective Disorders." It certainly complements the extensive review by Robert Hirschfeld and Susan Blumenthal of personality, life events, and other psychosocial factors in adolescent depression and suicide. It has implications for the important message of Felton Earls and Ada Jemison that affective illness and suicidal behavior are substantially different for American minorities than for the majority culture.

An important question is whether suicide can be predicted by observing risk factors. Several chapters describe results of longitudinal studies with implications for outcome of suicidal behavior and maladaptation among young people. Sheppard Kellam and C. Hendricks Brown show that young schoolchildren exhibit early signs for the expression of substance abuse and psychopathology 10 years later. Gene Smith outlines longitudinal research efforts to delineate correlates of dysphoric mood and suicidal ideation and acts.

Although clinical descriptions are not the main focus of

this book, they are not lacking. John Mack presents the most moving chapter, "Adolescent Suicide: An A chitectural Model," in which he synthesizes the relationships of a variety of factors involving the contextual, structural, and systems aspects of youth suicide. These concepts are made memorable by vignettes of the profound writings of a 14-year-old girl who committed suicide by hanging herself at home. Mack's thinking is complemented by the theoretical discussion of Tim Brennan on adolescent loneliness. Brennan suggests that "the very process of becoming a person, of assuming an individual identity and a separate sense of self, leads to the experience of isolation and loneliness" (p. 187). He notes that "the inability to deal with separation and its associated loneliness is implicated in certain aspects of developmental failure in adolescence" (p. 188) and that failure can increase risk for suicidal behavior. Also in keeping with clinical concerns, Robert Arnstein describes his experiences as a consultant to a college mental health clinic and the implications for suicide prevention among this group of students.

An illuminating chapter by Ernest Gruenberg contains an excellent overview of research strategies useful for planning prevention trial studies. He discusses differences between clinical treatment trial studies and prevention trial studies. A practical application of the integration of these concepts is presented by Eva Deykin in her chapter "Adolescent Suicide and Self-Destructive Behavior: An Intervention Study." She discusses a promising intervention strategy with suicidal 13–17-year-olds evaluated in the emergency services of two urban hospitals in Massachusetts.

Finally, this book is conceptualized within the context of a historical perspective. It is an outgrowth of the national alarm about youth suicidal behavior. In fact, a great lesson is to be learned from the publication of this informative volume. The impact of federal support for mental health programs in the 1970s, the subsequent effores of Julius Richmond, who was Surgeon General of the Public Health Service and is the author of the introduction to this book, and the leadership of Gerald Klerman, as Administrator of the Alcohol, Drug Abuse, and Mental Health Administration, were aimed at creating greater awareness of preventive strategies in coping with mental illness. In 1977, the suicide rates for adolescents and young adults were at peak levels. However, the Boston conference occurred in 1982, 5 years after the maximum suicide rates. Furthermore, this book was published in 1986, 4 years after that conference. The timing of the publication of this book is an example of a common trend: most of our efforts to respond to the needs to prevent youth suicide have drastically lagged behind the time of greatest need to intervene. Nevertheless, this book is the product of a continuity of philosophy and commitment to promote healthy mental functioning in young people. It is fortunate that this book is now available and can be a stimulus for continued efforts to understand and prevent the tragedy of youth suicide.

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Culture and Depression: Studies in the Anthropology and Cross-Cultural Psychiatry of Affect and Disorder, edited by Arthur Kleinman and Byron Good. Berkeley, University of California Press, 1985, 510 pp., \$45.00.

This is an excellent multidisciplinary book that seeks answers to two questions: 1) Would the life style in some

societies protect one from depressive illness? 2) Does depressive illness look quite different in some cultures? The anthropological view is that there are differences not only in depression as mood but also in symptoms of depressive illness. Examples are that in some African societies dreams may be the first signs of illness, suggesting that a witch may be attacking one's vital essence. In American Indian groups, however, hearing voices of relatives who have died is considered normal.

Dramatic differences have been found in the expression of bodily complaints with depressive illness. Nigerians may complain about "ants keep creeping in parts of my brain" while Chinese may complain of exhaustion of the nerves or of their heart being squeezed. According to this book, the fact that symptoms which serve as the criteria for depressive illness vary across cultures raises problems for the crosscultural validity of depressive illness.

The contributions of the anthropologists and psychologists are noteworthy. Obeyesekere suggests that if the culture-bound syndrome of semen loss were to be operationalized and used as a part of a survey instrument in Europe or the United States, it would be considered foolishly ethnocentric. Spero Manson reports a study of depressive experience among American Indians, using illness beliefs among American Indians to arrive at a culturally sensitive definition. Morton Beiser describes the results of his research among Africans in Senegal, Indo-Chinese refugees in Canada, and Americans in midtown Manhattan: factor analysis showed that somatization and depression are separate entities, and somatization may be more commonly associated with anxiety than with depression. Anthony Marsella, a psychologist in the World Health Organization (WHO) depression study center in Hawaii, reviews the WHO international studies, which tend to support the view of a core depressive disorder. Finally, Kleinman and Kleinman describe the studies of patients in Hunan Medical College in China in which were found a close relationship between depression and "neurasthenia.'

Arthur Kleinman is one of the international experts in cross-cultural psychiatry. He has done excellent research with Chinese in Taiwan and in China. With Byron Good, he has produced an excellent resource book. It is highly technical, due to the various disciplines of the contributors, but nonetheless extremely valuable.

This book is recommended for all American psychiatrists in view of the increasing multiculturalism of the people of the United States. All of us need to know more about the ways that culture may shape the manifestation of symptoms and psychiatric disorders. The book does not definitively answer questions in this area, but it asks many pertinent questions pointing us in the right direction.

JOE YAMAMOTO, M.D. Los Angeles, Calif.

Depression: A Psychobiological Synthesis, by Paul Willner. New York, Wiley-Interscience (John Wiley & Sons), 1985, 577 pp., \$69.50.

When first asked to review this book, I was doubtful that a synthesis of psychological and biological data was currently possible. I also wondered about the value of a review of this material in book form because this area is so rapidly changing. After reading this work, I still doubt that a synthesis is possible, but I am very impressed with

the extraordinarily comprehensive review of the depression literature that Dr. Willner has provided. It requires a volume of this length.

Although the concept of the psychobiological model is elegant and complex, the term "psychobiological" is sometimes used as a convenient means of superficially covering all the theoretical bases. This book is not superficial. The bibliography alone—150 pages of approximately 3,000 references—is very extensive. The second chapter of the book, "On the Nature of Psychobiological Explanation," provides a very thoughtful discussion of the psychobiological model and an interesting critique of theories that focus on one aspect of depression. Willner suggests, for example, that a knowledge of neurochemical events may be fundamental to understanding depression, but these concepts have little validity if they do not explain the physiological or psychological processes that they presumably control. He suggests that an adequate theory of depression has to consider events or processes in four domains: chemical, psychological, cognitive, and experiential. As Willner proceeds with his review he attempts to link one domain of research with another.

Investigators or clinicians interested in theories of depression will find this book interesting and useful. I found the sections on material with which I was less familiar intriguing and useful as a reference for further study. The book can serve an important "encyclopedic" function from this perspective.

My only serious criticism of this book is that the level of critical review varies considerably depending on the topic covered. The reviews of neurochemical research and animal models of depression are thorough and reflect a critical perspective. However, research findings in other areascognitive functioning, lateralization of emotional function, and findings in clinical areas, for example—are sometimes cited dogmatically even though they might be controversial or not well established. For example, Willner states that "MAOIs have proved to be of little value in endogenous depressions" (p. 57) and that "aggression and hostility are absent in bipolar depressions but are not uncommon among unipolar endogenous depressions and are usually present in neurotic depressions" (p. 124). It should not be surprising that a critical review of all areas of depression research is beyond the expertise of one individual, but this issue should be of concern to those interested in psychobiological models because this problem hinders the task of a broad synthesis. A critical review of the several domains of research in depression requires several experts, but conceptual models are usually developed by individuals. I wish the author had concluded the book with another, more philosophically oriented chapter addressing this issue. Specifically, how can a synthesis of a broad area of information be achieved while expertise is maintained within specialized areas?

The title suggests that the author will ultimately attempt a synthesis of the theories and data he reviews. Whether he intended to or not, Willner successfully demonstrates that research in depression covers a vast domain, that connections between different areas of research are just beginning to be made, and that a synthesis is not currently possible. I think the use of the word "synthesis" in the title is overly optimistic. In the last paragraph the author more accurately states, "The object of this book has been to provide a current and reasonably comprehensive review of the psychobiology of depression." He has very successfully accomplished this.

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#### **DEMENTIA**

Modern Approaches to the Dementias, Part I: Etiology and Pathophysiology, edited by F. Clifford Rose. Basel, Karger, 1985, 221 pp., \$75.75.

Modern Approaches to the Dementias, Part II: Clinical and Therapeutic Aspects, edited by F. Clifford Rose. Basel, Karger, 1985, 195 pp., \$68.25 (\$143.00 for the set).

These volumes contain the results of a conference held in London in 1983. The papers are short and for the most part clearly written summaries of research on Alzheimer's disease. Most of the authors are European leaders in the field and thus provide American psychiatrists with new ideas and different perspectives.

In part one, Constantinidis reports on the Geneva autopsy series and suggests that presenile-onset Alzheimer's disease is transmitted as a dominant and senile-onset Alzheimer's as a recessive genetic trait. He also suggests an autosomal dominant form of multi-infarct disease. These cases often begin with a depressive or bipolar mood disorder and with other behavioral abnormalities not explained by the cognitive disorder. Since the pathology often involves the frontal and temporal lobes selectively, this disorder is yet another model, along with stroke, Huntington's disease, and Parkinson's disease, for the study of the neuropathological substrate of mood and behavioral abnormalities. In addition, Constantinidis presents the novel idea that Pick's disease is due to an excess of zinc that is found in the urine, blood, and brain of the patients and even suggests some improvement with the use of EDTA. Replication of this finding should be attempted in a multicenter study.

Kidd et al. review the amyloid story, noting that Alzheim-

er's disease is a spectrum of disorders—from dementia pugilistica, which is characterized by abundant tangles but no plaques, to Jakob-Creutzfeldt disease, which contains in some cases plaques but no tangles. They note that in Alzheimer's disease amyloid is found in three locations: 1) in neurons, in the form of tangles, which they propose are related to amyloid, 2) in blood vessel walls, and 3) in plaques.

Wisnieski et al. write that Alzheimer's disease is a slow viral infection of a genetically susceptible host. Several authors note the evidence suggesting that Alzheimer's disease might be a cortical disorder with secondary degeneration of the nucleus basalis of Meynert and other subcortical structures.

Bowen et al. report on the results of a brain biopsy and post-mortem study leading to the observation that the striatum degenerates in Alzheimer's disease. This finding suggests that an important descending cortical system mediated by glutamate is affected, leading to tangle formation in addition to the well-known ascending systems from the basalis and the locus ceruleus which lead to plaque formation.

In part two, several authors, including the Mohs and Davis group, review the effects of cholinergic agonists and esterase inhibitors. Thirty percent of subjects can be helped with these drugs. The differences between physostigmine responders and nonresponders constitute an important area for research.

These books can be recommended as a guide to research in the area, when combined with the January 1986 issue of the *British Medical Bulletin* devoted to Alzheimer's disease.

MARSHAL F. FOLSTEIN, M.D. Baltimore, Md.

Reprints of Book Forum reviews are not available.

#### AIDS-Related Complex Presenting as Psychosis

SIR: Since the first reports in 1981, acquired immune deficiency syndrome (AIDS) has become an expanding major public health problem; more than 12,000 cases and 6,000 deaths have been reported to date (1). Increasingly, physicians in diverse specialties will have to become alert to unusual presentations of this illness.

The human t-cell lymphotropic (leukemia) virus-type III (HTLV-III), also known internationally as HIV (human immunodeficiency virus), is believed to be the causative agent. This virus has a predilection for neural tissue, and as many as 40% of AIDS patients will have neurologic complications at some point in their illness (1). Neuropathologic data of autopsied adult AIDS patients have shown that the cortex is relatively spared; abnormalities predominate in the white matter and subcortical and limbic areas (2). The latter areas are believed to govern emotional experience, so it should not be too surprising that 82.7% of patients with the AIDS-related complex were found to have mood disturbances (3). There have been a few reports (4) of psychosis occurring as a later complication of AIDS but none, to our knowledge, of psychosis without dementia as the presenting feature of CNS infection with the AIDS retrovirus.

We report the case of a 48-year-old homosexual Caucasian male with no previous psychiatric history who was admitted to a psychiatric hospital for the abrupt onset of acute paranoid psychosis. He showed positive results on tests of his serum and CSF for HTLV-III.

The chief complaint of Mr. A, who had worked as a supervisor on the railroads for the past 21 years, was his overwhelming distress about "being zapped by his neighbors' heat flashes and laser-type devices" for the preceding 3 weeks. These symptoms and his experience of hearing voices in his right ear, which he attributed to his neighbors' having put a "bug" there, began at the time he had an attack of allergic rhinitis, with otitis in his right ear, which resolved in 2 days.

Information gained from the patient, his family, and friends revealed no history of previous psychiatric disorder, drug abuse, or exposure to industrial toxins and no family history of mental illness. Serial mental status examinations and neuropsychological tests (Luria-Nebraska) 1 week apart demonstrated no organic signs, no cognitive defects (other than an insignificant [less than 1 SD] visuospatial processing problem), and no deterioration of mental functioning on repeat testing.

Review of systems, physical examination, laboratory tests (CBC with differential, blood chemistry, endocrine and liver-function tests, urinalysis, and RPR), and CAT and nuclear magnetic resonance scans revealed nothing to suggest AIDS, other systemic infectious illness, lymphadenopathy, or otorhinolaryngologic or neurologic disease. A urine screen detected no drugs.

Two spinal taps performed 3 days apart, before treatment with neuroleptic medications began, produced the following CSF findings, respectively: WBC, 7 and 8 cells/mm<sup>3</sup> with 89% and 100% lymphocytes and 0% and 11% monocytes; glucose, 56 and 68 mg/dl; and protein, 37 and 71 mg/dl, with no oligoclonal bands. Results of microscopy, serology, and cultures for syphilis, tuberculosis, cryptococcus, toxoplasma, herpes group, and all other viruses, including HTLV-III, were negative.

HTLV-III antibodies in blood and both CSF specimens, tested by enzyme-linked immunoabsorbent assay and, for confirmation, by radioimmunoassay (Western blot technique), were reactive.

The data we have presented in this case history support our contention that this patient was probably suffering from an organic psychosis without dementia caused by CNS infection with the HIV/HTLV-III agent. Intra-blood-brainbarrier synthesis of HTLV-III-specific IgG is considered good evidence of infection within the blood-brain barrier (5). The new Centers for Disease Control (CDC) classification system of HTLV-III infections includes group IV-B: neurological manifestations of dementia, myelopathy, and peripheral neuropathy, but not psychosis. Should forthcoming reports in the literature present findings similar to ours, the current CDC classification of HTLV-III infections may require revision to include psychiatric illness. Nonetheless, psychiatrists should consider in their differential diagnosis of mental disorders, including psychosis, this increasingly prevalent disease entity.

#### REFERENCES

- 1. Detmer WM, Lu FG: Neuropsychiatric complications of AIDS: a literature review. Int J Psychiatry Med 1986–1987; 16:21–29
- Navia BA, Cho ES, Petito CK, et al: The AIDS dementia complex. Ann Neurol 1986; 19:525-535
- Perry SW, Tross AS: Psychiatric problems of AIDS inpatients at the New York Hospital: preliminary report. Public Health Rep 1984; 99:200-205
- Rundell JR, Wise MG, Ursano RJ: Three cases of AIDS-related psychiatric disorders. Am J Psychiatry 1986; 143:777-778
- Resnick L, diMarzo-Veronese F, Schupbach J, et al: Intrablood-brain barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. N Engl J Med 1985; 313:1498–1504

BRIAN D. HALEVIE-GOLDMAN, M.D. STEVEN G. POTKIN, M.D. PAT POYOUROW, M.D. Orange, Calif.

# Trimipramine in the Treatment of Obsessive-Compulsive Disorder

SIR: Despite progress in other areas of psychopharmacology, the treatment of obsessive-compulsive disorder remains difficult. Although many antidepressant agents have been reported to be effective in this disorder, these findings have been inconsistent (1). Numerous authors have reported a

specific antiobsessional effect of the substituted form of imipramine, clomipramine (2); it has also been demonstrated that this antiobsessional effect is independent of any antidepressant effect in patients with this disorder (2). Unfortunately, clomipramine has not been approved for use in the United States.

Trimipramine, another substituted form of imipramine, is currently approved by the Food and Drug Administration. Hypothesizing that its similarity to clomipramine might indicate that it has an antiobsessional effect, we recently successfully treated a patient with obsessive-compulsive disorder with trimipramine.

Andrew, a 12-year-old prepubertal boy, developed an acute onset of obsessive thoughts about religion and "going to hell," as well as a compulsion to read the Bible in various situations, approximately 6 months before coming for treatment. The thoughts and compulsions were recurrent and intrusive; although the boy viewed them as irrational, he was unable to suppress them. Over the next 2 months he became progressively more depressed and developed insomnia, anorexia, anhedonia, deterioration in school performance, and passive suicidal ideation, followed by lack of interest in personal hygiene and delusions of worthlessness. He was initially treated with imipramine, 150 mg/day, and trifluoperazine, 10 mg/day. The combined plasma concentration of imipramine and desipramine was 270 ng/ml.

Andrew's reality testing improved during the first week, and his neurovegetative symptoms resolved over the next 5 weeks. Although his mood became considerably less depressed, the religious obsessions persisted. Alprazolam, 4 mg/day, was added to his drug regimen without effect.

After 8 weeks of therapy, the imipramine was discontinued and trimipramine, 150 mg/day, was substituted. Within 2 weeks there was a dramatic resolution of Andrew's obsessions, compulsive behavior, and anxiety. Subsequently, the alprazolam and trifluoperazine were discontinued without any increase in symptoms. The beneficial effect of trimipramine persisted over the next 5 months; the patient last reported only an occasional obsessive thought.

We are unaware of any previous reports in the literature of the use of trimipramine in obsessive-compulsive disorder. Since this patient did indeed manifest depressive symptoms, it might be argued that the antidepressant effect of trimipramine was solely responsible for his improvement. However, the patient initially manifested obsessive-compulsive—not depressive—symptoms, and these depressive symptoms clearly remitted with imipramine, leaving the pure obsessive-compulsive syndrome, which proved responsive to trimipramine.

The mechanism of antiobsessional action of clomipramine is not at all clear. It has been speculated that inhibition of serotonin reuptake may be crucial, as clomipramine is particularly potent in this regard (3). However, Insel et al. (4) demonstrated that the potent serotonin reuptake inhibitor zimelidine is ineffective in obsessive-compulsive disorder and concluded that antiobsessional effect is not related to serotonin reuptake inhibition. Also, trimipramine is not a particularly strong serotonin reuptake inhibitor (3). Both trimipramine and clomipramine exhibit dopamine D<sub>2</sub> receptor blockade—perhaps 10 times that of imipramine (5). One could speculate that this may be related to antiobsessional effect. Clearly, further investigation is needed to elucidate the

neuropharmacologic effect of tricyclic antidepressants in obsessive-compulsive disorder.

#### REFERENCES

- Ananth J: Pharmacotherapy of obsessive-compulsive disorder, in Obsessive-Compulsive Disorder. Edited by Mavissakalian M, Turner SM, Michelson L. New York, Plenum, 1985
- 2. Flament MF, Rapoport JL, Bert ĆJ, et al: Clomipramine treatment of childhood obsessive-compulsive disorder. Arch Gen Psychiatry 1985; 42:977–983
- 3. Richelson E, Pfenning M: Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes. Eur J Pharmacol 1984; 104:277–286
- Insel TR, Mueller EA, Alterman I, et al: Obsessive-compulsive disorder and serotonin: is there a connection? Biol Psychiatry 1985; 20:1174–1188
- Richelson E, Nelson A: Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984; 230:94–102

ROBERT J. BARTUCCI, M.D. JONATHAN T. STEWART, M.D. JOHN P. KEMPH, M.D. Gainesville, Fla.

# Clonidine and Clomipramine in Obsessive-Compulsive Disorder

SIR: Clonidine hydrochloride has been shown to be effective in the treatment of Gilles de la Tourette's disease (1, 2), markedly alleviating the obsessional symptoms. There was also a report in this journal that clonidine was effective in obsessive-compulsive disorder (3). We report three cases of obsessive-compulsive disorder, meeting *DSM-III* criteria, in which treatment with a combination of clonidine and anti-depressants was successful.

Adam, a 16-year-old youth, had a 12-month history of obsessions consisting of suicidal thoughts and murderous thoughts about his family. He recognized these thoughts as absurd and attempted to resist them, which increased his anxiety. The obsessions impaired his school performance and he became socially withdrawn. His mood became depressed, but there were no biological features of depression. He had no past psychiatric history and no family history of psychiatric problems.

Adam was given clonidine, 0.25 mg/day, and clomipramine, 20 mg/day. Within 3 months he was much improved. His dose of clonidine was increased to 0.25 t.i.d. and the dose of clomipramine to 10 mg t.i.d.; within another 2 months he was symptom free. He remained free of symptoms at 12-month follow-up.

Ms. B, a 41-year-old woman, had an 8-month history of obsessions, which consisted, for instance, of wondering, "What does food taste like to other people?" She had a 10-year history of obsessions, remitting and exacerbating at annual intervals. Her sister also suffered from obsessions. She was put on a regimen of clomipramine, 40 mg/day; a month later this was increased to 60 mg/day, and flupenthixol, 5 mg/day, was added. She began to improve. Her dose of clomipramine was increased to 100 mg/day, but she developed symptoms of giddiness, so the dose was reduced to 75 mg/day. Little improvement had occurred after 6 months. She was then given clonidine, 0.25 mg b.i.d., and the flupenthixol was discontinued. She began to

improve in 48 hours. She was seen 4 months later, by which time her obsessions had virtually disappeared. She was still symptom free 16 months later.

Mr. C was a 31-year-old man with an 8-year history of depressive feelings and obsessions. The obsessions consisted of haunting visions of a boy's face. He was given tranylcypromine, which improved his mood but not his obsessions. The tranylcypromine was discontinued, and he was given clonidine, 0.25 mg b.i.d., and clomipramine, 20 mg/day. Within 1 month he was much improved. At 18-month follow up he had remained symptom free for the whole of that period.

Our experience with these cases led us to conduct a double-blind, placebo-controlled trial of clonidine in patients with obsessive-compulsive disorder, which we intend to report shortly.

#### REFERENCES

- Cohen DJ, Young JG, Nathanson JA, et al: Clonidine in Tourette's syndrome. Lancet 1979; 2:551-553
- Cohen DJ, Detlor J, Young JG, et al: Clonidine ameliorates Gille de Tourette syndrome. Arch Gen Psychiatry 1980; 37: 1350–1357
- 3. Knesevich JW: Successful treatment of obsessive-compulsive disorder with clonidine. Am J Psychiatry 1982; 139:364–365

M.S. LIPSEDGE, M.PHIL., F.R.C.PSYCH. WILLIAM PROTHERO, M.B., M.R.C.PSYCH. London, England

#### Interaction Between Thioridazine and Naltrexone

SIR: We would like to report an adverse interaction between thioridazine and naltrexone in two patients. Both patients had been stabilized on thioridazine for many months without reporting any major side effects, but they experienced intense lethargy after naltrexone was added to their regimens when they participated in a pilot project to assess the efficacy of naltrexone for tardive dyskinesia.

Mr. A, a 54-year-old black man with a history of chronic paranoid schizophrenia, had been stabilized on 50 mg t.i.d. of thioridazine for several years. He had tolerated the medicine without any side effects except a moderate but stable tardive dyskinesia. He gave written consent to participate in a pilot research protocol involving a naloxone challenge test (0.8 mg i.v.) and 50 mg/day of naltrexone for 2 weeks. At the time of the study he was not taking any other medicine. The naloxone challenge test was uneventful, but after receiving his second dose of naltrexone, Mr. A became very sleepy and lethargic. He slept long hours and did not wish to be awakened for his meals. He became paranoid and fearful when awake. There were no other changes in his mental status examination and no other sign of increased neuroleptic level, such as extrapyramidal side effects. The severe lethargic state cleared up 12 hours after the last dose of naltrexone.

Mr. B, a 34-year-old white man who had had a chronic schizoaffective disorder for 14 years and severe tardive dyskinesia for 7 years, had been given trials of several neuroleptics over the past 13 years. Before his current admission, he had been maintained on 200 m.g. t.i.d. of

thioridazine for 12 months without any detectable side effects. He gave written consent to undergo a naloxone challenge test (0.8 mg i.v.) followed by 100 mg of naltrexone every other day for 2 weeks. As in the case of Mr. A the naloxone challenge test was uneventful, but after receiving the second dose of naltrexone, Mr. B became lethargic and slept for 36 hours. He managed to wake up only for oral fluid intake and urination. There were no additional changes in his mental status examination, and, as in the first case, no other signs of neuroleptic toxicity were observed. His condition also cleared up 12 hours after the last dose of naltrexone.

Thioridazine, similar to other aliphatic phenothiazines, possesses sedative effects upon acute administration. Tolerance to this sedation, however, usually develops with chronic use. Neither of the patients reported here exhibited any sedative effects before participating in the study.

Naltrexone, an opioid antagonist with minimal agonistic effects, has rarely been reported to produce sedation (1). It is possible that naltrexone inhibits the degradation of thioridazine, thus increasing plasma concentration of thioridazine and leading to a thioridazine toxic state, or there may be a pharmacodynamic interaction that has little bearing on thioridazine levels. Unfortunately, we did not determine these two patients' thioridazine plasma levels.

Since naltrexone is now available for the rehabilitation of opioid-dependent individuals, and some of these people may be concurrently taking neuroleptics, we believe clinicians should be aware of this presumed interaction.

#### REFERENCE

 Meyer MC, Straughn AB, Lo MW, et al: Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. J Clin Psychiatry 1984; 45(9, section 2): 15-19

> IRADJ MAANY, M.D. CHARLES P. O'BRIEN, M.D., PH.D. GEORGE WOODY, M.D. Philadelphia, Pa.

# Mediation of "Calcium Antagonist" Effects by Dopamine Receptor Blockade

SIR: Thomas L. Walsh, M.D., and colleagues (1) described the usefulness of verapamil and nifedipine but not diltiazem in two patients with Tourette's disorder.

There is an explanation for reports of behavioral effects with some calcium channel antagonists but not with others. Verapamil appears to have dopamine receptor blocking activity. In 1982 Cronin (2) reported that verapamil displaced <sup>3</sup>H-spiperone binding in porcine anterior pituitary. This was consistent with reports of prolactin release and galactorrhea in women receiving verapamil (3, 4). Johnson et al. (5) showed reversal of dopamine effects by verapamil in an isolated rabbit ear artery preparation. Diltiazem and nitrendipine, however, did not antagonize dopamine.

We examined the mood and neuroendocrine effects of diltiazem in a single-blind study of bipolar patients and normal control subjects. The diltiazem was given in a dose of 5–15 mg i.v. over 10 minutes, and a significant decrease in heart rate was seen. However, there were no mood effects in four normal volunteers and two euthymic bipolar patients. We also found no effect of intravenous diltiazem in a

hypomanic patient tested on two occasions. Diltiazem did not affect prolactin or cortisol levels.

Verapamil has been reported to be effective in some manic patients (6). The available evidence is consistent with the hypothesis that the effects of verapamil in psychiatric patients are mediated through dopamine receptors rather than calcium channel blockade. It has yet to be demonstrated that other calcium antagonists such as diltiazem, which do not appear to block dopamine receptors, have effects on mood or psychiatric symptoms under controlled conditions.

#### REFERENCES

- Walsh TL, Lavenstein B, Licamele WL, et al: Calcium antagonists in the treatment of Tourette's disorder. Am J Psychiatry 1986; 143:1467–1468
- Cronin MJ: Some calcium and lysosome antagonists inhibit <sup>3</sup>H-spiperone binding to the porcine anterior pituitary. Life Sci 1982; 30:1385–1389
- 3. Grospietsch G, Fenske M, Konig A, et al: Effects of the uterine relaxant fenoterol and the calcium antagonist verapamil on plasma prolactin concentrations in mid-pregnancy. IRCS Medical Science, 1979, p 6
- Gluskin LE, Strasberg B, Shah JH: Verapamil-induced hyperprolactinemia and galactorrhea. Ann Intern Med 1981; 95:66-67
- Johnson CE, Steinsland OS, Scriabine A: Dopamine antagonist effect of verapamil on isolated perfused rabbit ear artery. J Pharmacol Exp Ther 1983; 226:802–805
- Dose M, Emrich HM, Cording-Tommel C, et al: Use of calcium antagonists in mania. Psychoneuroendocrinology 1986; 11: 241–243

JOHN NURNBERGER, JR., M.D., PH.D. Indianapolis, Ind. SUSAN SIMMONS-ALLING, M.S.N. Bethesda, Md.

#### Increased Libido with Trazodone

SIR: I was especially interested in the report by Nanette Gartrell, M.D., of increased libido in women receiving trazodone (1) because of my experience in treating a depressed male bipolar patient over the course of 20 months.

Mr. A, a 36-year-old single white man, had had his first manic episode at the age of 24. Since that time he had had five psychiatric hospitalizations, four for mania and one for severe depression. When lithium maintenance was started 5 years previously, Mr. A's manic episodes occurred less frequently, but his depressions remained severe and refractory to treatment. Three months before I began to treat him he had been hospitalized briefly for a manic episode that had responded quickly to antipsychotics. Before that, he had been euthymic for 4 months. He came for treatment with vegetative signs of depression (anergy, decreased concentration, hypersomnolence, decreased appetite, severe psychomotor retardation), social withdrawal, and suicidal ideation. In addition to lithium, 2100 mg/day, with blood levels of 0.8-1.2 meq/liter, he was already taking trazodone, 450 mg/day in divided doses. He had had trials of at least five other antidepressants before starting trazodone 2 years previously. Although aware of the risk of priapism with trazodone, he reported that it had not interfered with his sexual functioning but had, in fact, increased his sexual desire even while he was depressed.

Mr. A's trazodone was increased to 600 mg/day and his

increased sexual desire persisted. Occasionally, he would have sex with his usual partner; usually he would masturbate several times daily. He was never socially hypersexual, nor did he exhibit any other indications of mania, hypomania, or mixed manic state, but he remained moderately to severely depressed. Subsequently, Mr. A had adequate trials of both nortriptyline and phenelzine; when he was taking these medications his libido returned to the usual low depressive levels, which was quite distressing to him. Even though his depression responded partially to phenelzine, Mr. A wanted to return to trazodone treatment specifically because of the increased libido effect. Trazodone was restarted and, again, his sexual desire increased dramatically and remained increased. He continued to prefer trazodone for this reason, even though it was not a particularly effective antidepressant for him.

This patient's increased libido could have been an unusual presentation of a hypomanic state (2). However, the increased libido occurred while he was clinically depressed and showed no other signs of mania or hypomania. Further, treatment with a tricyclic for 1 month and a monoamine oxidase inhibitor for almost 2 months did not produce any hypomanic symptoms; when trazodone was restarted the increased libido recurred. Another explanation might be that trazodone exerted a more direct pharmacologic stimulation of sexual desire, as Dr. Gartrell suggested. While regulation of sexual desire remains poorly understood, animal studies have associated increased dopamine with sexual stimulation (3), and trazodone does exhibit dopaminergic activity (4, 5).

#### REFERENCES

- Gartrell N: Increased libido in women receiving trazodone. Am J Psychiatry 1986; 143:781–782
- Warren M, Bick PA: Two case reports of trazodone-induced mania. Am J Psychiatry 1984; 141:1103–1104
- Buffum J: Pharmacosexology: the effects of drugs on sexual function. J Psychoactive Drugs 1982; 14:5–41
- Roccatagliata G, De Cecco L, Rossato P, et al: Trazodone intravenously administered and plasma prolactin levels. Int Pharmacopsychiatry 1979; 14:260–263
- 5. Garratini S: Biochemical studies with trazodone. Mod Probl Pharmacopsychiatry 1974; 9:29

GREER SULLIVAN, M.D. Los Angeles, Calif.

#### Long-Term Effects of Incest

SIR: The inferences drawn by Judith Herman, M.D., and associates in "Long-Term Effects of Incestuous Abuse in Childhood" (1) seem unjustified by the data they presented. They proposed "to delineate the range of long-term outcomes" and identify "persistent symptoms and difficulties," but their literature review and data presentation repeatedly suggested that there was a causal relationship. Although this is a compelling argument, it cannot be shown by the data collected. Like most case history data, theirs can only pose hypotheses, not answer them (2).

They described two samples: 152 of 930 women surveyed in the San Francisco area who reported sexual abuse in childhood and 53 female outpatients in a short-term therapy group for incest victims. The authors pointed out that the two samples could not be properly compared but then proceeded to compare them! They also calculated chi-

squares on data (their table 2) that represent subjects more than once (187 "occurrences" in 152 subjects) and are therefore not appropriate for the chi-square test.

The larger community sample could have been used to meaningfully explore the specific aftereffects of such abuse, but it was not. For instance, the authors reported complaints from abused women concerning negative feelings about men, sex, and themselves; generalized feelings of anxiety and mistrust; difficulties in forming or maintaining relationships; and current sexual problems. Surely these same complaints could have been found in some women among the remainder of the sample who were not abused. If the entire sample had been asked the same questions, then the hypothesis could easily have been tested by chi-square, but this was not done.

The authors emphasized in their discussion that all the abused women were upset by their experiences, but more striking was the fact that more than 18% were not very upset or were not upset at all. One wonders why not. Although about 50% of the sample were not aware of any residual effects or reported that these were only slight, the authors stated that this was "optimistic" and suggested—without data—that perhaps the informants were not themselves aware of the long-term consequences!

Finally, the authors did not seem to recognize that just because subjects attributed symptoms to childhood abuse, this does not really shed any light on actual causal factors. Research on the long-term consequences of childhood sexual abuse is badly needed, but it must be methodologically sound if it is to lead to knowledge that can protect future generations.

#### REFERENCES

- 1. Herman J, Russel D, Trocki K: Long-term effects of incestuous abuse in childhood. Am J Psychiatry 1986; 143:1293–1296
- Altman H, Evenson RC: Marijuana use and susequent psychiatric symptoms: a replication. Compr Psychiatry 1973; 14: 415–420

RICHARD C. EVENSON, PH.D. St. Louis, Mo.

#### Coerced Outpatient Treatment

SIR: In "Rights, Wrongs, and the Dilemma of Coerced Community Treatment" (1), Jeffrey L. Geller, M.D., argued convincingly that a sizable number of individuals who do not obtain psychiatric care voluntarily, and who become dangerous without psychiatric treatment, might adjust well to life outside the hospital if taking psychotropic drugs regularly were made a condition of their staying free. Dr. Geller deserves praise for his honest, thoughtful account of how he provided "enforced care." He noted that coercive outpatient treatment raises a number of moral questions; I would like to note two issues that he did not include in his excellent discussion.

1. When Dr. Geller wrote of "the plight of the . . . chronic psychiatric patient in the community," he implied that coerced treatment could be imposed on psychiatric patients whose relapses might endanger only themselves. However, physicians in all specialties encounter patients who undergo repeated, costly hospitalizations and endanger their lives because they fail to follow treatment recommendations: diabetics who don't take insulin properly, emphysema patients who won't stop smoking, heart failure patients who eat a lot of salt, etc. Wouldn't arguments that justify out-

patient commitment of psychiatric patients justify similar coercion for all medical patients whose noncompliance endangers themselves? What is it about competent, unconditionally discharged psychiatric patients (like those Dr. Geller "coerced") that differentiates them from other medical patients with chronic, relapsing illnesses? Would nonpsychiatric physicians want to assume the authoritarian role that Dr. Geller advocates for psychiatrists?

2. Dr. Geller suggested that a major difficulty in coercing patients involves balancing their autonomy against any paternalistic duties which (presumably benevolent) physicians may have. However, it is consistent with giving liberty rights the highest priority to think that mental illness may justify overriding those rights (2). Unfortunately, psychiatrists, lawyers, and ethicists have often focused debate on the quality of a psychiatric patient's autonomy instead of resolving the questions of why, when, and how a psychiatric patient's autonomy can be rightfully restricted.

Psychiatrists often possess important general or particular knowledge regarding the likelihood of a recurrence of psychiatric illness and associated dangerous behavior. However, society usually gives courts the power to deprive rational persons of their liberty. When psychiatrists coerce patients with threats of commitment—even if this is indisputably in their best interest—patients' due process rights are violated. The North Carolina commitment statute cited by Dr. Geller puts the responsibility for forcing outpatient treatment on the courts, where that responsibility belongs.

Physicians nowadays can make available to patients therapeutic tools with enormous power to better their lives, but whether patients have a legal *obligation* to use those tools is a matter for courts, not doctors, to decide.

#### REFERENCES

- 1. Geller JL: Rights, wrongs, and the dilemma of coerced community treatment. Am J Psychiatary 1986; 143:1259–1264
- Rawls J: A Theory of Justice. Cambridge, Mass, Harvard University Press, 1971

DOUGLAS MOSSMAN, M.D. Charleston, S.C.

#### Dr. Geller Replies

SIR: I thank Dr. Mossman for his praise and address the two issues he raises.

Dr. Mossman draws a parallel between psychiatric patients who endanger only themselves and medical patients who endanger themselves by failing to comply with the clinical management of their disorder. This analogy is problematic. Society has not created a system of enforced care for medical patients, whereas it has done so for psychiatric patients. Commitment of a psychiatric patient for mental illness and dangerousness on the basis of that mental illness may occur independent of the patient's competency. Since psychiatrists operate in a system that not only sanctions involuntary inpatient treatment of mentally ill individuals but also sanctions preventive confinement of those individuals (1), the leap to outpatient commitment is not one that segregates the psychiatric patient from all others who are ill. Rather, it extends the imposition of treatment from inpatient settings to outpatient settings. The debate on involuntary psychiatric treatment, independent of the locus of treatment, is ongoing and has generated an extensive literature of its

own—produced by psychiatrists (2), philosophers (3), and lawyers (4).

Dr. Mossman takes issue with my arrogation of power in the (potential) deprivement of patients' liberty. It should be clear from the article that I, too, believe that the authority for involuntary outpatient commitment should be through state statutes and the courts' enforcement of those statutes. However, if the practicing psychiatrist doubts that noninterference is consistently respectful of autonomy and believes from clinical experience that enforced treatment is the only efficacious treatment for a specific patient, should he or she be required to attempt to treat the patient voluntarily once again? To do so follows too closely the advice one character gave to another in *Leaving Cheyenne* (5):

"She's made mistakes," he said, "So have I and so have you."

"At least I ain't made the same ones over and over again," I said.

"Why not? You might as well make them you're used to as to make new ones all the time. It don't do no more damage."

#### REFERENCES

- Dershowitz A: The origins of preventive confinement in Anglo-American law, part II: the American experience. Cincinnati Law Review 1974; 43:781–846
- 2. Stone AA: Psychiatric abuse and legal reform: two ways to make a bad situation worse. Int J Law Psychiatry 1982; 5:9–28
- Callahan JC: Liberty, beneficence, and involuntary confinement. J Med Philos 1984; 9:261–293
- Morse SJ: A preference for liberty: the case against involuntary commitment of the mentally disordered. California Law Review 1982; 70:54–106
- McMurtry L: Leaving Cheyenne. New York, Popular Library, 1963

JEFFREY L. GELLER, M.D., M.PH. Worcester, Mass.

#### Obsessive-Compulsive Disorder and Psychosis

SIR: Thomas R. Insel, M.D., and Hagop S. Akiskal, M.D., are to be complimented for their bold and thorough excursion into the somewhat murky territory of obsessive-compulsive disorder and psychosis (1). They identified 1) patients who begin with obsessive-compulsive symptoms and then become overtly and chronically schizophrenic, 2) another group who are so imprisoned by their obsessive-compulsive symptoms that reality ceases to dominate and who are, for all practical purposes, psychotic, and 3) a group—of greatest interest to me—which they described in the section Reactive Transition From Obsessions to Delusions.

In this section I did not think the authors sufficiently documented their statement that "follow-up studies demonstrate that as many as 20% of patients with obsessive-compulsive disorder become psychotic." A recent examination of the literature on brief psychosis in typical obsessive-compulsive disorder had led me to conclude that it is a very uncommon development. The authors quoted Sir Aubrey Lewis (2) as noting, "The surprising thing is not that some obsessionals become schizophrenic, but that only a few do so." From my study of the literature and from experience over four decades, I would extend Sir Aubrey's statement:

the surprising thing is not that some obsessionals have brief psychotic episodes, but that only a few do so. Further comment would be appreciated.

#### REFERENCES

- Insel TR, Akiskal HS: Obsessive-compulsive disorder with psychotic features: a phenomenologic analysis. Am J Psychiatry 1986; 143:1527–1533
- Lewis A: Problems of obsessional illness. Proc R Soc Med 1935; 29:324–336

MYRON G. SANDIFI.R, M.D. Lexington, Ky.

#### Drs. Insel and Akiskal Reply

SIR: The percentage of obsessive-compulsive disorder patients who become psychotic remains unclear. In table 1 of our article, we cited eight follow-up studies suggesting that the incidence of schizophrenia was quite low in obsessive-compulsive disorder but that between 1.5% and 16.7% of patients with this disorder develop some form of psychosis. In one study, 20% of the patients were described as "doubtfully psychotic" at the outset. These figures are not entirely conclusive because the studies we cited used varying criteria for the diagnosis of obsessive-compulsive disorder and usually were not explicit in their descriptions of psychosis.

Still, we would not agree with Dr. Sandifer's comment that psychosis is "a very uncommon development." A recent follow-up study of 100 patients with obsessive-compulsive disorder diagnosed by DSM-III criteria found that 6% had delusions, 4% had hallucinations, and 1% had formal thought disorder (1). In that study, 80% developed depression and 16% showed what the authors described as a "deteriorative course." These more recent data agree with our summary of the earlier follow-up studies in that 1) a substantial proportion of "typical" patients with obsessive-compulsive disorder showed evidence of psychotic features at follow-up, and 2) those who became psychotic were more likely to show an affective than a schizophrenic pattern.

The point of our paper was to eschew a narrow association between obsessive-compulsive syndrome and neurosis. We believe the syndrome is best viewed as a spectrum of disorders, some of which share features of both affective and paranoid psychoses.

#### REFERENCE

 Rasmussen SA, Tsuang MT: Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 1986; 143:317–322

> THOMAS R. INSEL, M.D. Betbesda, Md. HAGOP S. AKISKAL, M.D. Memphis, Tenn.

#### Pisa Syndrome, or Pleurothotonus

SIR: In their letter "The Pisa Syndrome During Mainte nance Antipsychotic Therapy" (1), Nina Guy, M.D., and associates used a catchy label to describe a tardive dystonic reaction that is marked by tonic flexion of the trunk to one side along with a slight rotation. I find the label dehuman-

izing and prefer the older and admittedly duller name of "pleurothotonus," which has almost disappeared from the psychiatric literature.

This striking disorder is not rare, as is claimed by Ekbom et al. (2) or as is implied by its absence from recent psychopharmacology textbooks. It is more common than opisthotonus, which is regularly mentioned. I have seen six cases of pleurothotonus in my 11 years' work in two state hospitals. The patients were all more than 50 years old, some were male and some were female, and all suffered from chronic schizophrenia. As in acute dystonic reactions, which have been associated more commonly with high-potency neuroleptics (3), all six patients were taking high-potency antipsychotic medications. They all responded to a decrease in dosage and/or the addition of antiparkinsonian medication.

#### REFERENCES

- 1. Guy N, Raps A, Assael M: The Pisa syndrome during maintenance antipsychotic therapy (letter). Am J Psychiatry 1986; 143:1492
- 2. Ekbom K, Lindholm H, Ljungberg L: New dystonic syndrome associated with butyrophenone therapy. Zeitschrift für Neurologie 1972; 202:94-103
- 3. Swett C Jr: Drug-induced dystonia. Am J Psychiatry 1975; 132: 532-534

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#### Dr. Guy and Associates Reply

SIR: In our letter we described the tonic flexion of the trunk to one side along with slight rotation and compared it to the Tower of Pisa. We do not find the label "Pisa syndrome" dehumanizing. Even in the Bible, people were compared to towers: "Thy neck is like the tower of David builded for an armoury, whereon there hang a thousand bucklers, all shields of mighty men" (The Song of Solomon 4:4).

Saxena (1) described one case of Pisa syndrome in 1986, and Yassa (2) reported two cases in 1985. The case we described was the only one we had seen during 13 years of work with chronic schizophrenic patients who were treated with neuroleptic drugs. We think it is important to report these rare cases of the Pisa syndrome, which appeared in patients less than 50 years old, and to be aware of the treatment needed by those patients.

#### REFERENCES

- 1. Saxena S: Tardive dystonia and Pisa syndrome (letter). Br J
- Psychiatry 1986; 149:524

  2. Yassa R: The Pisa syndrome: a report of two cases. Br J Psychiatry 1985; 146:93-95

NINA GUY, M.D. AVI RAPS, M.D. MARCEL ASSAEL, M.D. Rehovot, Israel

#### Pseudologia Fantastica

SIR: The literature on pseudologia fantastica is sparse and has not been reviewed in English since Wiersma (1), over 50 years ago. Nevertheless, pseudologia fantastica is still used,

for example, as one of the diagnostic symptom triad (with peregrination and disease simulation) for Munchausen syndrome (2); it was described recently in the article "Pseudologia Fantastica in the Borderline Patient" by Scott Snyder, M.D. (3). Dr. Snyder's paper is important for its description of the possible dynamic underpinnings of pathological lying in borderline patients. However, it appears that he used the terms "pathological lying" and "pseudologia fantastica" interchangeably, thereby making the proposed psychodynamic formulations less specific. For example, some of the lies Dr. Snyder described seemed overtly manipulative or aggressive.

Others have also used pseudologia fantastica interchangeably with pathological lying (4), but it may be more useful to view pseudologia as one type of pathological lie. Wiersma's (1) distinction is useful in this regard. He described lying as a continuum, with "normal" lying at one end and pseudologia, as an extreme form of pathological lying, at the other. On the basis of his review, pseudologia fantastica is characterized by the telling of stories without, or entirely disproportionate to, discernible motive and with such zeal that the liar may convince himself of their truth. In so doing, the liar impairs his discrimination of fantasy from reality. While a defective or incomplete distinction between fiction and reality must be present, pseudologia is distinct from delusions in that when pseudologues' attention is energetically brought to the subject, they can acknowledge, at least partly, the falseness of their utterings (1).

Pseudologia fantastica is a fascinating phenomenon that has been reported in a variety of contexts including organic impairment (5) and primary character disorders. For this reason the distinction between pseudologia and other pathological lies, although difficult, is important.

#### REFERENCES

- 1. Wiersma D: On pathological lying. Character and Personality 1933; 2(1):48-61
- 2. Bursten B: On Munchausen's syndrome. Arch Gen Psychiatry 1965; 13:261-268
- 3. Snyder S: Pseudologia fantastica in the borderline patient. Am J Psychiatry 1986; 143:1287-1289
- 4. Healy W, Healy MT: Pathological Lying, Accusation, and Swindling. Patterson Smith Reprint Series in Criminology, Law Enforcement, and Social Problems. Montclair, NJ, Patterson Smith, 1969
- 5. Pankratz L: A review of the Munchausen syndrome. Clin Psychol Rev 1981; 1:65-78

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#### Dr. Snyder Replies

SIR: I welcome the comments of Drs. King and Ford. They stress the point that pseudologia fantastica should be viewed as an extreme form of pathological lying and provide one of the original definitions of this syndrome.

The definition of pseudologia fantastica that is found in the opening paragraph of my paper is practically identical to the one provided by Wiersma. The question then becomes, To what degree did the patients described in the four case reports meet the cited criteria for pseudologia without being "manipulative or aggressive"? Cases 1 and 4 clearly meet either definition for pseudologia. In case 2, the patient may

have been expressing her anger toward men through her pseudologia, but she had no obvious personal gain to be realized from manipulating the facts of the alleged rape. She fulfilled all other clinical characteristics of pseudologia. The patient in case 3 was somewhat manipulative but gained little in practical terms from the arrival of her parents. Otherwise she met all the criteria for pseudologia.

By definition, borderline patients tend to be "manipulative and aggressive." Under either definition, the patients described in these cases fulfilled the criteria for pseudologia fantastica.

SCOTT SNYDER, M.D. Athens, Ga.

#### Systems and the Structure of Meaning

SIR: Michael Alan Schwartz, M.D., and Osborne P. Wiggins, Ph.D., in their article on systems and the structure of meaning (1), suggested ways to reduce the "bloomin' confusion" of understanding everything from subatomic particles to social systems. Within the assumptions and rhetoric they employed, their arguments seem reasonable. The problem is how to evaluate whether what they said is true. Any number of theoretical approaches can explain; how should we choose?

In the systems they delimited as following causal process—from subatomic particles through the nervous system—we validate theories by empirically testing hypotheses within the scheme of the natural sciences, and there is little disagreement about how to do that. However, the "higher" level—from the person to the biosphere—they said, we understand (verstehen) by grasping the meaning of things.

The problem is, how do we validate such understanding? If Mr. Glover tells us that he got upset when the resident missed his artery because he lost confidence in the staff, that seems quite a reasonable explanation; but what if we want to go further and explain why Mr. Glover might be more sensitive to such a situation than others, or if we wish to descend to some "deeper" level of understanding as typified by various psychodynamic schools? How do we choose which explanations to accept? It's all very nice to say that we need to know a lot about the person to avoid an incorrect explanation, but I doubt if this resolves the question. Clinicians with comparable knowledge of a person's "empirical condition" come to quite different explanations. I don't see how this wider-ranging theoretical structure will help us in our task of deciding among all the various ways of understanding people, once we have ruled out, as Jaspers does, using the scientific method accepted in the natural sciences (2). Must we discard the scientific method of proving a hypothesis by predictive experiments? I don't see why we must follow Jasper in making this sharp dichotomy. It is conceivable that explanations about persons and social systems can lead to empirically verifiable hypotheses, e.g., the distinguished work of Phillips (3) showing that publicity about suicide leads to an increase in suicides. This type of research will not plumb the soul and explain everything, but it can increase our understanding of why people act as they

On the other side, strict scientific investigation within the natural sciences is not without some degree of subjectivity and intuitive understanding, since any way we conceive of a physical system and an experiment must be based on how we structure and think of the world. And, of course, since

quantum mechanics came along we have had to realize that there is no strict separation between the observer and the observed—that we don't just empirically evaluate what is "out there" as though we were not ourselves part of "out there."

Jaspers's dichotomy doesn't seem ironclad. We should not give up our struggle to validate theories within the realm of persons and social systems by experiment, and we should not be unaware of the "soft" intuitive aspects of "hard science."

#### REFERENCES

- Schwartz MA, Wiggins OP: Systems and the structuring of meaning: contributions to a biopsychosocial medicine. Am J Psychiatry 1986; 143:1213-1221
- Jaspers K: General Psychopathology. Translated by Hoenig J, Hamilton MW. Chicago, University of Chicago Press, 1963
- Phillips DP: Suicide, motor vehicle fatalities and the mass media: evidence toward a theory of suggestion. Am J Sociology 1979; 84:1150-1173

ARTHUR RIFKIN, M.D. Elmhurst, N.Y.

#### Drs. Schwartz and Wiggins Reply

SIR: Dr. Rifkin objects to a strict dichotomy between understanding and explanation, which we in fact never endorsed. Our views of science, however, do differ from his. For us, all scientific investigation employs a critical attitude, a commitment to search for as much evidence as possible regarding the truth or falseness of any given claim (1-3). In addition, the different domains of scientific investigation present themselves to us evidentially in very different ways; for this reason, these different domains are best illuminated by different scientific methods. The more abstract sciences, such as physics, are better served by more abstract methods, such as mathematical and statistical methods (i.e., explanation), while the more concrete sciences, such as psychology, are better served by more concrete methods (i.e., understanding). But we admit no dichotomy here. Understanding, for example, also plays a role in physical sciences. Physiologists studying laws governing the functions of rods and cones in vision would never even have been able to localize their field of study if they had not already understood that eyes are for seeing. Moreover, explanation plays a role in the human sciences. However, while we admire Phillips's work on suicide as much as Dr. Rifkin does, we find that such explanations are by themslves rather empty and abstract. They may tell us a great deal about suicides in general, but they tell us very little about Mr. Smith's suicide last Friday. What is gained with explanation is precision and exactitude, but what is lost is the fullness and concreteness of phenom-

And what of understanding, which seems too ambiguous for Dr. Rifkin? In fact, Jaspers's "laws of meaningfulness" do help us surmount some of this ambiguity (4). They do negate some ways of understanding—for example, ways unsupported by any direct evidence. Furthermore, Jaspers's laws provide the inclusion criteria (depth, complexity, connectedness, and vividness) and exclusion criteria (the need to resort to many ad hoc assumptions and extraconscious mechanisms). Dr. Rifkin seems to want more precision than this, yet here he demands too much. If we examine human meaning with a critical attitude, we see that multiple interpretations of phenomena are in fact grounded in directly

given evidence (2). The meaning of a human experience is in fact ambiguous. Nonetheless, not just any interpretation will do, because many fail to be grounded in evidence altogether and instead require ad hoc hypotheses and cumbersome extraconscious mechanisms. While some may wish to find the one true interpretation, the critical attitude discloses many. Such ambiguity may seem unsatisfactory, but, contrary to what many think, precision and exactitude are not requirements of genuine science. Rather, the requirement is to remain faithful to what the evidence discloses. It is even a violation of the data to force them into precise models when they are ambiguous. We like to call such a dogmatic stance "the Procrustes complex," in honor of the mythological figure who first demanded precision at all costs. A truly scientific psychiatry will avoid such a stance and admit a healthy pluralism of methods (5).

#### REFERENCES

- Husserl E: Formal and Transcendental Logic. Translated by Dorian Cairns. The Hague, Martinus Nijhoff, 1969
   Schwartz MA, Wiggins OP: Science, humanism and the nature
- Schwartz MA, Wiggins OP: Science, humanism and the nature of medical practice: a phenomenological view. Perspect Biol Med 1985; 28:331-361
- Schwartz MA, Wiggins OP: Typifications: the first step for clinical diagnosis in psychiatry. J Nerv Ment Dis 1987; 175:65– 77
- 4. Jaspers K: General Psychopathology. Translated by Hoenig J, Hamilton MW. Chicago, University of Chicago Press, 1963
- McHugh PR, Slavney PR: The Perspectives of Psychiatry. Baltimore, Johns Hopkins University Press, 1983

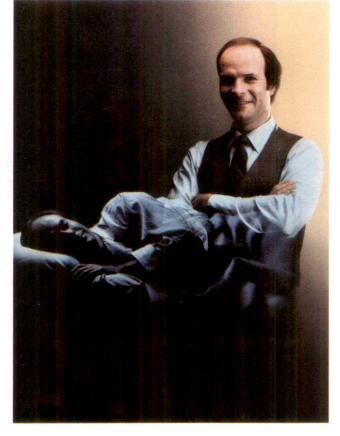
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Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

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ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the phar $macologic\ activity\ of\ HALCION,\ e.g.,\ drows in ess,\ dizziness,\ or\ lightheadedness.$ 

	HALCION	Placebo	
Number of Patients	1003	997	
% of Patients Reporting:			
Central Nervous System			
Drowsiness	14.0	6.4	
Headache	9.7	8.4	
Dizziness	7.8	3.1	
Nervousness	5.2	4.5	
Lightheadedness	4.9	0.9	
Coordination Disorder/Ataxia	4.6	0.8	
Gastrointestinal			
Nausea/Vomiting	4.6	3.7	

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations. diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

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- 1. Stone AA: Mental Health and Law: A System in Transition. Rockville, Md, NIMH, 1975, pp 102–103
- Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
- 3. Rubinow DR, Post RM, Pickar D, et al: Relationship between urinary-free cortisol and CSF opiate binding activity in de-

pressed patients and normal volunteers. Psychiatry Research (in press)

 McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979

 Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

 Smythe GA, Compton PJ, Lazarus L: Serotoninergic control of human growth hormone secretion: the actions of L-dopa and 2bromo-α-ergocyptine. Excerpta Medica International Con-

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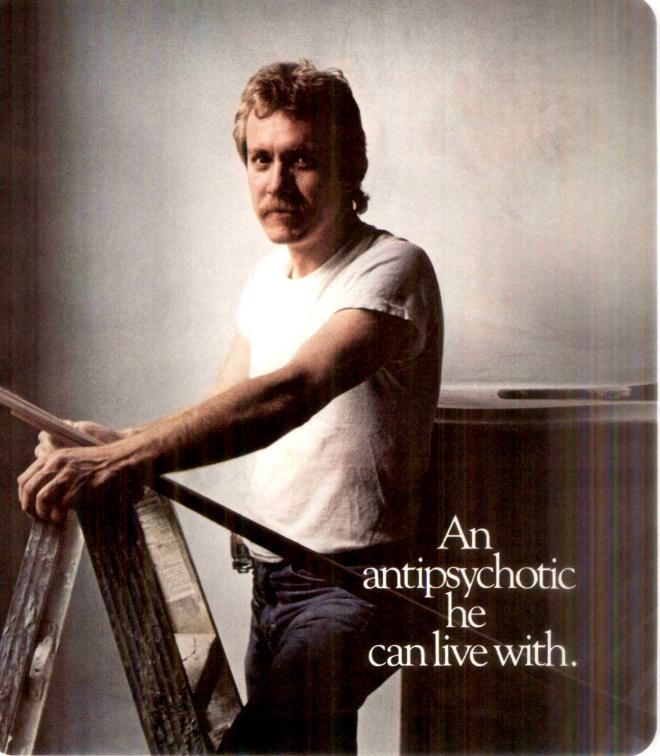
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cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug. 
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Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions). Where patients are participating in activities requiring complete mental alertness (e.g., Where patients are participating in activities requiring complete mental alertness (e.g., Where patients are participating in activities requiring complete mental alertness (e.g., Where patients are participating in activities requiring complete mental alertness (e.g., Where patients are participating in activities requiring complete mental alertness (e.g., Where patients a

detection, please refer to the sections on Information for Patients and Adverse Reactions). Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

\*\*Usage in Pregnancy:\*\* The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

\*\*Usage in Children:\*\* The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

\*\*Precautions:\*\* While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

\*\*Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

\*\*Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive selizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

\*\*Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration.\*\* If hese drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents

reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and b urred vision have occurred in some instances.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and b urred vision have occurred in some instances. Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exificiative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, bilary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the 1 wave and appearance of a wave tentatively identified as a bilid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients pre

noted. Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions,

noted. Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia. \*\*Jardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the \*\*Warnings\*\* section and below.\*\*
The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, lace, mouth, ips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely. The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear allogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

\*\*Endocrine Disturbances\*\* Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

\*\*Urlinary Disturbances\*\*\* Retention, inconlinence.

\*\*Others\*\* Hypergyrexia. Behaviora effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigm

How Supplied: Serentil® Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine

Serentil® Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Serentil® Ampuls, for intramuscu ar administration: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20 and 100.

Serentil® Concentrate, for oral acministration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0 61% by volume. Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing

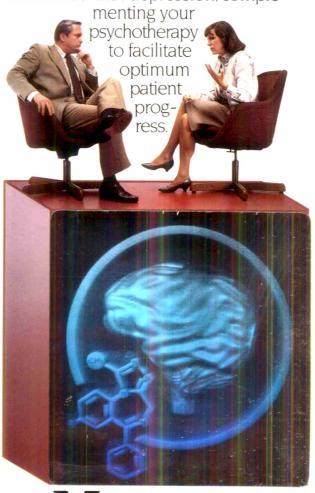
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# A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.

The incorporation of a triazolo ring to the basic benzodiazepine structure clearly differentiates Xanax from other benzodiazepines.

Xanax effectively relieves anxiety associated with depression, comple-





COMPLEMENTS AN EFFECTIVE THERAPEUTIC ALLIANCE



# A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.



#### XANAX Tablets (alprazolam) @

#### CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

#### WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

#### **PRECAUTIONS**

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with ben-

zodiazepines have been reported. Drug/ Laboratory Test Interactions: No consistent pattern for a specific drug or specific test. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. Labor and Delivery: No established use. Nursing Mothers: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

#### **ADVERSE REACTIONS**

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia,

dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

#### DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S J-6338 January 1987

#### Upjohn

THE UPJOHN COMPANY Kalamazoo, Michigan 49001 USA The Biology of Moral Systems, by Richard D. Alexander. New York, Aldine de Gruyter, 1987, 280 pp., \$34.95; \$16.95 (paper).

Migraine and Epilepsy, edited by Frederick Andermann, M.D., F.R.C.P.(C), and Elio Lugaresi, M.D. Boston, Butterworths, 1987, 422 pp., \$59.95.

The Psychology of Happiness, by Michael Argyle. New York, Methuen, 1987, 245 pp., \$47.50; \$14.95 (paper).

The Resource Book: Directory of Organizations, Associations, Self-Help Groups, and Hotlines for Mental Health and Human Services Professionals and Their Clients, by Robert L. Barker. New York, Haworth Press, 1986, 144 pp., \$17.95.

Brief Therapy: Short-Term Psychodynamic Intervention, by Gregory P. Bauer, Ph.D., and Joseph C. Kobos, Ph.D. Northvale, N.J.,

Jason Aronson, 1987, 303 pp., \$25.00.

Psychotherapy of Schizophrenia, by Gaetano Benedetti, M.D. New York, New York University Press (Columbia University Press, distributor), 1987, 239 pp., \$42.50.

When You Face the Chemically Dependent Patient: A Practical Guide for Nurses, by Judy Bluhm, R.N., M.A. St. Louis, Mo., Ishiyaku EuroAmerica, 1987, 203 pp., \$22.50 (paper).

The Psychopharmacology and Treatment of Schizophrenia: British Association for Psychopharmacology Monograph 8, edited by P.B. Bradley and S.R. Hirsch. New York, Oxford University Press, 1986, 441 pp., \$69.00.

Coping With Threatened Identities, by Glynis M. Breakwell. New

York, Methuen, 1986, 211 pp., \$29.95.

Medical Equipment and Quality of Care, edited by David Bushelle, M.A.; Ode Richard Keil, M.S., C.C.E., technical consultant. Chicago, Joint Commission on Accreditation of Hospitals, 1987,

35 pp., \$25.00 (paper).

Teach Your Child Decision Making: An Effective 8-Step Program for Parents to Teach Children to Solve Everyday Problems and Make Sound Decisions, by John F. Clabby, Ph.D., and Maurice J. Elias, Ph.D. Garden City, N.Y., Doubleday & Co., 1986, 332 pp., \$16.95; \$8.95 (paper).

The Development of Play, by David Cohen. Washington Square, N.Y., New York University Press (New York, Columbia Univer-

sity Press, distributor), 1987, 181 pp., \$32.00.

Mental Handicap and Sexuality: Issues and Perspectives, by Ann Craft, B.S.C.(Econ), C.Q.S.W. Turnbridge Wells, England,

Costello, 1987, 262 pp., £10.95 (paper).

Clinical Pharmacology in Psychiatry: Selectivity in Psychotropic Drug Action: Promises or Problems? edited by S.G. Dahl, L.F. Gram, S.M. Paul, and W.Z. Potter. New York, Springer-Verlag, 1987, 281 pp., \$53.90.

Talking With Your Aging Parents, by Mark A. Edinberg. Boston, Shambhala (New York, Random House, distributor), 1987, 213

pp., \$16.95.

Healthy High-Fiber Cooking, by Jeanette P. Egan. Tucson, Ariz., HP

Books, 1987, 157 pp., \$9.95 (paper).

Sleep, Aging and Related Disorders, edited by W. Emser, D. Kurtz, and W.B. Webb. Basel, Karger, 1987, 157 pp., \$69.50.

Battered Women Who Kill: Psychological Self-Defense as Legal Justification, by Charles Patrick Ewing. Lexington, Mass., Lexington Books (D.C. Heath & Co.), 1987, 169 pp., \$24.95.

Cocaine: Clinical and Biobehavioral Aspects, edited by Seymour Fisher, Allen Raskin, and E.H. Uhlenhuth. New York, Oxford University Press, 1987, 249 pp., \$24.95.

Selected Writings of Selma Fraiberg, edited by Louis Fraiberg. Columbus, Ohio State University Press, 1987, 678 pp., \$39.50;

\$17.50 (paper).

Issues in Psychiatric Classification: Science, Practice and Social Policy, edited by Alfred M. Freedman, M.D., Richard Brotman, Ph.D., Irving Silverman, Ph.D., and David Hutson, N.S.W. New York, Human Sciences Press, 1986, 244 pp., \$29.95.

Cognitive Therapy: Applications in Psychiatric and Medical Settings, edited by Arthur Freeman and Vincent B. Green vooc. New York, Human Sciences Press, 1987, 227 pp., \$34.35: \$16.95

Advancing Frontiers in Alzheimer's Disease Research edited by George G. Glenner, M.D., and Richard J. Wurtman, N. ...). Austra, University of Texas Press, 1987, 262 pp., \$22.50.

The Uses of Countertransference, by Michael Gork 1, Ph.D. Northvale, N.J., Jason Aronson, 1987, 301 pp., \$27.50.

Attempted Suicide: A Practical Guide to Its Nature and Management, 2nd ed., by Keith Hawton and Jose Catalan. New York. Oxford University Press, 1987, 205 pp., \$17.95 (pap r

The Shaping of Modern Psychology, by L.S. Hearnshaw London, Routledge & Kegan Paul, and New York, Methuen, 1987, 409

pp., \$36.95.

Alcohol and Drug Abuse Handbook, edited by Rolanc E. Herrington, M.D., George R. Jacobson, Ph.D., and David G. Benzer, D.O. St. Louis, Mo., Warren H. Green, 1987, 470 pg. \$55.00.

Birth Order Roles and Sibling Patterns in Individual and Family Therapy, by Margaret M. Hoopes, Ph.D., and James Vi Harper, Ph.D. Rockville, Md., Aspen, 1987, 213 pp., \$29.50: \$17.95 (paper).

A Guide to Dynamics of Feminist Therapy, edited by Dons Howard, Ph.D. New York, Harrington Park Press, 1986, 338 pp., \$14.95

How to Use Intervention in Your Professional Practice: A Guide for Helping-Professionals Who Work With Chemical Dependents and Their Families. Minneapolis, Minn., Johnson Institute Books, 1987, 110 pp., \$8.95 (paper).

Schizophrenia: A Fresh Approach, by Gwen Howe. Nor + Pomfret, Vt., David & Charles, 1986, 170 pp., \$13.95 (paper)

Preventing Malpractice in Long-Term Care: Strategics for Risk Management, by Marshall B. Kapp, J.D., M.P.H. N.w York, Springer Publishing Co., 1987, 241 pp., \$27.95.

Behavior, Bias, and Handicaps: Labeling the Emotionally Disturbed Child, by Judy W. Kugelmass. New Brunswick, N.J., Transaction

Books, 1987, 159 pp. \$34.95.

Movement Disorders, edited by C. David Marsden, F.R.S., D.Sc., M.Sc., M.B.B.S., M.R.C.Psych, F.R.C.P., and Stanley John, M.D. Boston, Butterworths, 1987, 458 pp., \$45.00.

Stature and Stigma: The Biopsychosocial Development of Short Males, by Leslie F. Martel and Henry B. Biller, Lexington, Mass., Lexington Books (D.C. Heath & Co.), 1987, 111 pp., >21.00.

Dreams: Night Language of the Soul (1985), by Phoebe VicDonald. New York, Continuum, 1987, 228 pp., \$10.95 (pape-

The Art of Aging: A Celebration of Old Age in Western Art, by Patrick McKee, Ph.D., and Heta Kauppinen, Ph.D. New York, Insight Books (Human Sciences Press), 1987, 187 pp., 519.95.

Brainfood: Nutrition and Your Brain (1986), by Brian I.G. Morgan, Ph.D., and Roberta Morgan. Tucson, Ariz., Ecdy Press,

1987, 192 pp., \$7.95 (paper).

Poetry as Therapy, edited by Morris R. Morrison, Ph.D. New York, Human Sciences Press, 1987, 224 pp., \$29.95.

The Marginal Self: An Existential Inquiry Into Narcissis n, by René J. Muller. Atlantic Highlands, N.J., Humanities Iress International, 1987, 222 pp., \$15.00.

Affective Disorders in the Elderly, edited by Elaine Muray, M.D., M.R.C.Psych. New York, Churchill Livingstone (Wire Plains, N.Y., Longman, distributor), 1986, 230 pp., \$48.00.

Origins of Human Aggression: Dynamics and Etiology, edited by Gerard G. Neuman, Ph.D. New York, Human Sciences Press, 1987, 191 pp., \$29.95.

Dear Doctor: A Personal Letter to a Physician, by Charles E. Odegaard. Menlo Park, Calif., Henry J. Kaiser Family Founda-

tion, 1986, 172 pp., no price listed (paper).

Consultation-Liaison Psychiatry: The Psychiatric Clinics of North America, vol. 10, number 1, March 1987, edited by Donald Oken, M.D. Philadelphia, W.B. Saunders Co., 1987, 150 pp., no price listed.

Modern Biotechnology and Health: Perspectives for the Year 2000, edited by Manuel Elkin Patarroyo, John B. Zabriskie, and Diego Pizano-Salazar. Orlando, Fla., Harcourt Brace Jovanovich, 1987, 217 pp., \$35.00.

Laws and Policies Affecting Adolescent Health, by John M. Paxman and Ruth Jane Zuckerman. Geneva, World Health Organization,

1987, 300 pp., \$29.40 (paper).

A New Age: Problems and Potential, by Kenneth R. Pelletier. San Francisco, Robert Briggs Associates, 1985, 42 pp., \$3.95 (paper).

Psychiatric Differential Diagnosis, by Jeremy M. Pfeffer and Gillian Waldron; with Dr. J.C. Cookson. New York, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1987, 193 pp., \$27.50 (paper).

The Artist as Therapist, by Arthur Robbins, Ed.D., A.T.R. New York, Human Sciences Press, 1987, 222 pp., \$29.95.

101 Common Therapeutic Blunders: Countertransference and Counterresistance in Psychotherapy, by Richard C. Robertiello, M.D., and Gerald Schoenewolf, Ph.D. Northvale, N.J., Jason Aronson, 1987, 294 pp., \$27.50.

The Royal College of Psychiatrists, by Henry R. Rollin. London, Royal College of Psychiatrists, 1987, 15 pp., £2.00 (paper).

Clinical Treatment of the Violent Person, edited by Loren H. Roth,
 M.D., M.P.H. New York, Guilford Press, 1987, 260 pp., \$30.00.
 Untold Lives: The First Generation of American Women Psychologists, by Elizabeth Scarborough and Laurel Furumoto. New York,
 Columbia University Press, 1987, 226 pp., \$27.50.

Advances in Therapies for Children, by Charles E. Schaefer, Howard L. Millman, Steven M. Sichel, and Jane Riegelhaupt Zwilling. San

Francisco, Jossey-Bass, 1986, 430 pp., \$27.95.

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Russian Drinking: Use and Abuse of Alcohol in Pre-Revolutionary Russia, by Boris M. Segal. New Brunswick, N.J., Rutgers Center of Alcohol Studies, 1987, 366 pp., \$29.95; \$19.95 (paper).

The Somatizing Child: Diagnosis and Somatization Disorders, by Elsa Rosenfeld; with Norman Cohen, I Renken. New York, Springer-Verla

Sexuality and Medicine, vol. II: Ethiedited by Earl E. Shelp. Dordrecht Publishing Co., 1987, 272 pp., \$49

Approaches to Patient Care Assessme Report of the Sisters of Mercy Healt Sicher, Ph.D. Chicago, Joint Con Hospitals, 1987, 109 pp., \$30.00.

Memory and Brain, by Larry R. Squir sity Press, 1987, 294 pp., \$24.95; \( \)

Women and Cancer, edited by Steven Haworth Press, 1987, 277 pp., \$35

Psychotherapy and the Memorable Pa and William Kir-Stimor. New Yor pp., \$19.95.

Therapeutics for Aggression: Psycholotion, by Michael Thackrey, Ph.D. Press, 1987, 214 pp., \$29.95.

Handbook of Hypnosis for Professio New York, Van Nostrand Reinhok

The Variety of Dream Experience: Exing With Dreams, edited by Monta; Limmer, M.S. New York Continuu pp., \$19.95.

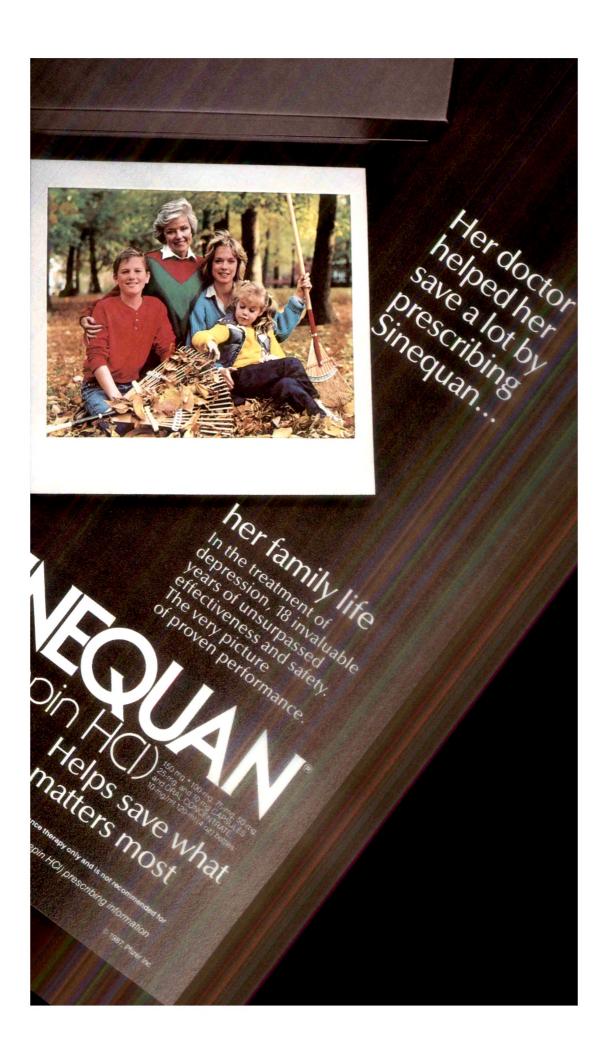
On Dreams and Death: A Jungian Int Louise von Franz; translated by F and Vernon Brooks. Boston, Shan House, distributor), 1987, 182 pp.,

The Hyperactive Child, Adolescent, Disorder Through the Lifespan, by Oxford University Press, 1987, 150

Post-Traumatic Stress Disorders: A Haby Tom Williams, Psy.D. Cincinna ans, 1987, 302 pp., no charge for s

The Laurel and Hardy Theory of Cc Wilson. San Francisco, Robert Bril \$2.95 (paper).

Mind Power: Getting What You War by Bernie Zilbergeld, Ph.D., and Arr Little, Brown and Co., 1987, 225 p



- BRIEF SUMMARY
  SINEQUAN® (doxepin HCI) Capsules/Oral Concentrate
  Indications. SINEQUAN is recommended for the treatment of:
  1 Psychoneurotic patients with depression and/or anxiety.
  2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with
- 3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).

  4. Psychotic depressive disorders with associated anxiety including involutional depression and
- manic-depressive disorders

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with antichinergic effects.

patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

\*\*Usage in Geriatrics\*\*: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

\*\*Usage in Pragnancy\*\*: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time in may vary and sependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohof: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant

Patients should also be cautioned that their response to alcohol may be potenhated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomato ogy occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and unitary retention have been reported. If they do not should be considered when prescribing SINEQUAN.

Anticoninergic Errects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends of isappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxa, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported coresponable.

Cardiovascular: Cardiovascular effects including hypotension and tachycarcia have been reported occasionally.

Allergic: Skin rash edema, photosensitization, and pruntus have occasionally occurred Hematologic: Cosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura. Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headacre have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN (doxepin HCI) administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

These are not mulcialize or advanced as symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day. In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose 300 mg/day.

300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day. The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for Initiation of treatment.

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not Anti-anxiety effect is apparent before the antidepressant effect. Optimal annidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms.

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.

2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and technicalities.

acinycarturas.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyper-thermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.

2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of troyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine saticylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN. respiratory depression. Dialysis and forced diuresis generally are overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request



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#### **LIBRIUM®**

chlordiazepoxide HCI/Roche (V 5-mg, 10-mg, 25-mg capsules
Before prescribing, please consult complete
product information, a summary of which follows:
Indications: Management of anxiety disorders;
short-term relief of anxiety symptoms, acute alcohol withdrawal symptoms, preoperative apprehension and anxiety. Usually not required for anxiety or tension associated with stress of everyday life. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: known hypersensitivity to the

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcahol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in aaministering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost arways be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to ar do

become pregnant.

Precautions: In the erderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally nor recommended, if combina-tion therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution

in patients with porphyria. Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasion ally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy **Usual Daily Dosage:** individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety disorders and symptoms, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d.

Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.) Supplied: Librium® (chlordiazepoxide HCI/Roche)

Capsules, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in and 300, tel:-20se® Jackages of 100, dividiable in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10. Libritobs® (chlordiazepoxide/Rcche) Roblets, 5 mg and 10 mg—bottles of 100 and 500; 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are Indistinguishable.











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## Breaking away

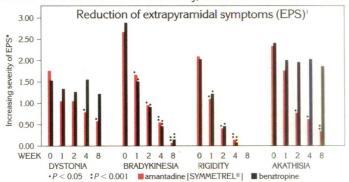


## rom the clutches of EPS

#### Effective control of extrapyramidal symptoms (EPS)

SYMMETREL® (amantadine HCl) has been proven clearly effective in controlling a broad range of extrapyramidal movement disorders. In a recent study, both SYMMETREL® and

benztropine "were equally effective in treating druginduced parkinsonism; however, amantadine [SYMMETREL®] proved somewhat more effective in reducing akathisia and recurrent dystonia."



\*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p

#### Fewer side effects than anticholinergics

Dramatically differentiating SYMMETREL® from anticholinergics is its favorable side effect profile. With fewer anticholinergic side effects, SYMMETREL® affords patients greater com-

fort—encouraging compliance with their antipsychotic regimen. SYMMETREL® is not metabolized and is mainly excreted in the urine. Care should be taken, however, in patients with renal impairment. SYMMETREL®. The more rational and safer¹ therapeutic choice in the control of EPS.

Incidence of anticholinergic side effects			
	% patients taking amantadine	% patients taking benztropine	
Dry mouth	7.4	41.6	
Blurred vision	2.6	26.5	
Nasal congestion	2.5	18.2	
Constipation	1.8	21.4	
Urinary hesitancy	1.3	7.1	

—adapted from Borison and Diamond, p  $43^{\,\rm I}$ 



Please see following page for brief summary of prescribing information





BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions: SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephallitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa, (-)-3-(3, 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL.

Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness

of vision should be cautioned against driving or working in situations where alertnes

is important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced it atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Since SYMME HELL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system

istimulants.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day, Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are: depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety; irritability; anorexia, nausea, and constipation; ataxia and dizziness (lightheadedness); livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a

Patients initially deriving benefit from SYMMETREL not uncommonly experience a tall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anti-cholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit. When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

Dosage for Drug-Induced Extrapyramidal Reactions: Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702

**Du Pont Pharmaceuticals** E.I. du Pont de Nemours & Co. (Inc.) Wilmington, Delaware 19898



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REFERENCE: 1. Borison RL, Diamond Bl: Treatment of extrapyramidal side-effects: Amantadine versus benztropine. World J Psychosynthesis (special), 1984-1985, pp 40-43.

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902-742-3541 Ext. 251.

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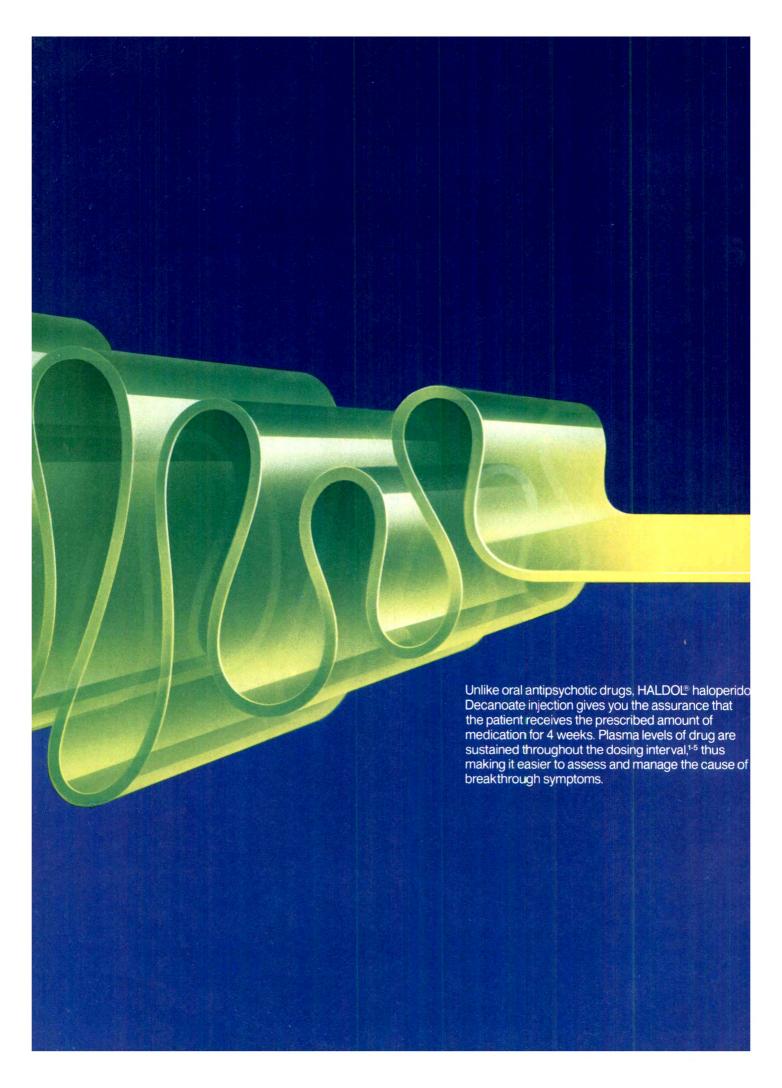
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#### Pharmacokinetic profile facilitates monthly dosing

Smooth, steady drug delivery has been shown to achieve efficacy equal to oral HALDOL, but at lower monthly doses.1 The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about 3 weeks.6

The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy have, at some time, been treated with, and have tolerated well, short-acting HALDOL in order to exclude the possibility of unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

#### Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

- References

  1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial

  1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: Efficacy, safety, and dosage equivalence. J Clin Psychopharmacol 1986;6(No. 1, Suppl.):30S-37S.
   Reyntjens AJM, Heykants JJP, Woestenborghs RJH, et al: Pharmacokinetics of haloperidol decanoate. Int Pharmacopsychiatry 1982;17:238-246.
   Deberdt R, Elens P, Berghmans W, et al: Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. An open multicenter study. Acta Psychiatr Scand 1980;62:356-363.
   Kissling W, Möller HJ, Walter K, et al: Double-blind comparison of

- Scand 1980;62:356-363.
  Kissling W, Möller HJ, Walter K, et al: Double-blind comparison of haloperidol decanoate and fluphenazine decanoate. Effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. *Pharmacopsychiatry* 1985;18:240-245.
  Roose K: Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. *Acta Psychiatr Belg* 1982;82:216-223.
  Nayak RK, Doose DR, Nair NPV. The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients (Submitted for publication).

Please see brief summary of prescribing information on next page.





The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling. Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, pletely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical

some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) Combined Use With Lithium: (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances. and/or physical abilities and on concomitant use with other substances

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential

promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation

assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia

in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase ficance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromyscular (extrapyramidal) reactions.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromususually mild to moderately severe and usually reversible. Other types of neuromus-cular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less fre-quently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-re-lated since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. How-ever, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL. should be gradually withdrawn. Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome It is suggested that all There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. Other CNS Effects: Insomaia, restlessness, anxiety, euphoria, agitation, rowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinercic drugs.

catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes. Hematologic Effects: Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell courts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. Liver Effects: Impaired liver function and/or jaundice. Dermatologic Reactions: Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. Endocrine Disorders: Lactation, breast engorgement, Dermatologic Reactions: Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration. Special Senses: Cataracts, retinopathy and visual disturbances. Other: Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdosage, see full prescrib-

ing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

11/10/86



### **CHARLES C THOMAS • PUBLISHER**

New! CLINICAL MANAGEMENT OF SUBSTANCE ABUSE PROGRAMS by Robert J. Craig. Focusing on the clinical management of programs, this unique work addresses the major steps of substance abuse treatment. The author examines patient assessment through the traditional diagnostic interview and psychological testing. Specific models of treatment are covered including the multimodal approach, a combined treatment approach, and matching treatment concepts to individual needs. Program evaluation activities and ways to reduce patient attrition are also discussed. '87, \$37.50

New! THE PSYCHOTHERAPIST-PATIENT PRIVILEGE: A Critical Examination by Daniel W. Shuman and Myron F. Weiner. The authors—a law professor and a psychiatrist—herein examine the role that privilege actually plays in therapy and its impact in litigation. They discuss such topics as professional ethics and confidentiality, psychosocial theory and privileged communication, legal foundations of privilege and professional secret, and the uses and limitations of empirical research in the law. '87, \$29.75

New! DISULFIRAM (ANTABUSE®) – A UNIQUE MEDICAL AID TO SOBRIETY: History, Pharmacology, Research, Clinical Use by Ronald W. McNichol, John A. Ewing, and Morris D. Faiman. Professionals will herein find a wealth of clinical information on an important treatment option for the disease of alcohol addiction—disulfiram (Antabuse®). This book encompasses a compilation of research on this unique medical aid, its pharmacodynamics, pharmacokinetics and toxicology. Sept. '87, about \$19.75

New! VIOLENCE PREDICTION: Guidelines for the Forensic Practitioner by Harold V. Hall. The dangerousness prediction process, forensic distortion analysis, a review of the accuracy and impact of literature and studies, dangerous prediction pitfalls, and training in violence prediction are among the topics discussed. Unique working appendices present actual prediction tasks, a checklist of violence factors, assessment report format, program evaluation format, and a needs assessment inventory. Sept. '87, about \$29.75

New! CRISIS INTERVENTION AND SUICIDE PRE-VENTION: Working with Children and Adolescents by Gary I. Crow and Letha I. Crow. Using the sequential approach to crisis intervention, this book develops a social interaction model which takes into consideration the whole child and his/her significant environment. The importance of communication, the factors and dynamics involved in a child's suicide, child abuse and its interrelatedness with family factors, and an extensive set of signs and symptoms of emotional difficulty are all discussed. '87, \$24.75

New! THE MURDERER AND HIS VICTIM (2nd Ed.) by John M. Macdonald. Drawing on decades of forensic psychiatric experience and on interviews with over 400 murderers, the author presents a penetrating look at people who kill and get killed. He reviews the circumstances of murder, probes the mind of the murderer, and describes the victim. Multiple personalities; fantasy games; Mafia hit men; investigation; sex, mass and serial murders; insane and juvenile murders; suicide; and many other topics all receive thorough coverage. '86, \$39.25

New! THE LAST STRAW: How To Benefit from Trigger Events in Your Life by Andrew J. DuBrin. Psychologically-oriented, this book examines why people finally take decisive action. After a brief introduction, each chapter deals with a major area of potential frustration including marriage and living together, health and appearance, sports and hobbies, consumer hassles, the boss and the company, hassles with employees, and career frustrations. Closing the text are six steps for making the most of these trigger events. '87, \$27.50

New! CLINICAL RESEARCH IN SCHIZOPHRENIA edited by Roy R. Grinker, Sr. and Martin Harrow. This book opens with a theoretical overview of schizophrenia. Research results follow on schizophrenic delusions, first rank symptoms, family relationship patterns, abnormal smooth pursuit eye movement, cognitive disorders, negative-deficit symptoms, and impaired perspective. Prognosis and outcome in schizophrenia are also discussed, and the text concludes with a review of the major aspects of the overall research program. July '87, about \$55.00

New! INVOLUNTARY CIVIL COMMITMENT OF THE MENTALLY ILL IN THE POST-REFORM ERA by Robert D. Miller. This book opens with a discussion of the three major definitional criteria for commitment—mental disorder, dangerousness, and need for treatment. It then examines the procedural criteria—right to counsel, to remain silent, to treatment, to least restrictive environment, to refuse treatment, and access to records. The final sections analyze the impact of changes in commitment statutes and future trends. Aug. '87, about \$42.75

New! BASIC HANDBOOK OF TRAINING IN CHILD AND ADOLESCENT PSYCHIATRY written and edited by Richard L. Cohen and Mina K. Dulcan. Experts herein review and describe an integrated approach to child psychiatric training and education. They discuss the background of child and adolescent psychiatry; guidelines for training in areas including child and adolescent psychopharmacology, developmental disabilities, pediatric consultation, and chief residencies; and examine approaches to program direction. Administrative and policy issues are also discussed. Sept. '87, about \$72.50

New! TECHNIQUES FOR DEALING WITH FAMILY VIOLENCE by Arlene Baxter. To help prevent violence and to assist families engaging in this violent behavior, professionals need to understand family dynamics and their social context. This text specifically addresses that need with discussions on societal attitudes, extent and types of family violence, family structure and roles, recognizing the symptoms of family dysfunction, risk assessment, developing and implementing a service plan, law enforcement involvement, the role of the courts, and community resources. Oct. '87, about \$24.75

KIDS GRIEVE TOO! by Victor S. Lombardo and Edith Foran Lombardo. At what age does a child understand the finality of death? Who should tell a child about the death of a loved one? When should a child attend a funeral? This practical, informative book answers these questions and more. The authors address television and a child's perception of death, the mourning process, and unresolved grief. A special question/answer section is also included. '86, \$17.75

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## THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 144, Number 8 August 1987

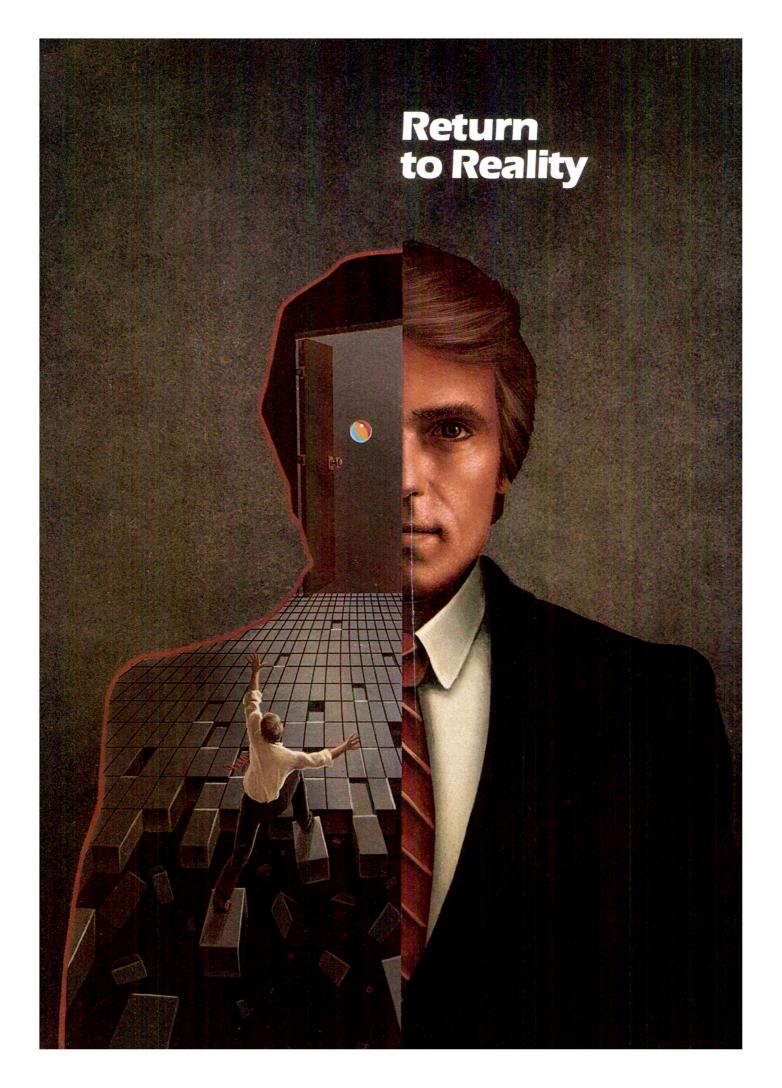
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Stelazine' shares the increased risk of extrapyramidal symptoms issociated with all high-potency neuroleptics. However, when incountered, these symptoms are generally readily controlled.

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Profession of the Profession o

>ntraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood scrasias; bone marrow depression; liver damage.

scraias; bone marrow depression; liver damage. **amings:** Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antiychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as
iration of treatment and total cumulative neuroleptic dose increase. Much less commonly,
esyndrome can develop after relatively brief treatment at low doses. There is no known
tatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment
ay suppress signs and symptoms of the syndrome and thereby mask the underlying disease
cess. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients
ho suffer from chronic illness that responds to neuroleptics and for whom alternative,
feature less harmful treatments are only available or appropriate in a viterior tecquiring chronic fective, less harmful treatments are not available or appropriate. In patients requiring chronic atment, the minimal effective dose and shortest duration of treatment should be sought. riodically reassess need for continued treatment. If signs and symptoms of TD appear, scontinuation of neuroleptics should be considered. [See PRECAUTIONS.]

scontinuation of neuroleptics should be considered. (See PRECAUTIONS.) enerally avoid using in patients hypersensitive [e.g., have had blood dyscrasias, jaundice] to any phenothiazine. Caution patients about activities requiring alertness [e.g., operating vehiles or machinery], especially during the first few days' therapy. Additive depressant effect is sisible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except hen essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, trapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose others received phenothiazines. There is evidence that phenothiazines are excreted in the east milk of nursing mothers. east milk of nursing mothers

**ecautions:** Since some patients chronically exposed to neuroleptics will develop tardive skinesia, it is advised that, if possible, full information about this risk be given to patients or eir guardians when chronic use is contemplated.

Le cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is ipaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If inal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, iemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with auroma.

estional tients with a history of long-term therapy with "Stelazine" and/or other neuroleptics should evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Suroleptic drugs cause elevated prolactin levels that persist during thronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of itential importance if neuroleptic drug use is contemplated in a patient with a previously etcled breast cancer. However, clinical and epidemiologic studies to date have not shown association between the chronic use of neuroleptic drugs and mammary tumorigenesis, is cautiously in persons who will be exposed to extreme heat.

ierothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce oha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases asma levels of both drugs. Concurrent use of phenothiazines may counteract antihyperten-

sive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenyloin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive "Stelazine" 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenor-rhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extra-pyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCI, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g. **phenothiazines:** Some adverse effects are more frequent or mitral insufficiency or pheochromocytoma).

initial insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities, altered cerebrospinal fluid proteins; cerebral edema, prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, pinapism, atonic colon, urinary-tretention, miosis and mydnasis, reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal), cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, Jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuna, menstrual irregulanties, galactorirhea, gynecomastia, false positive pregnancy tests, photosensitivity, tiching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactioid reactions, peripheral edema, reversed epinephrine effect; hyperprexia, mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal, EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupi cessation of high-dose therapy, NOTE. Sudden death in patients taking phenothiazines (apparently due to cardiac arrestor or asphysia due to failure of cough reflex) has been reported.

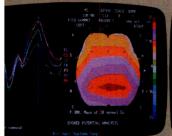
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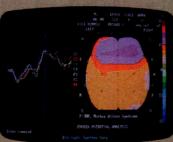
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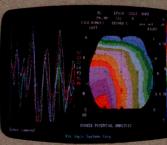
0 mean of 10 normal subjects



P-300 of patient with Morbus Wilson



FFT of EEG (EC), Morbus Wilson Syndrome



P-300 of patient with Alzheimer's Disease

#### Responsibility

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#### **Normative Data**

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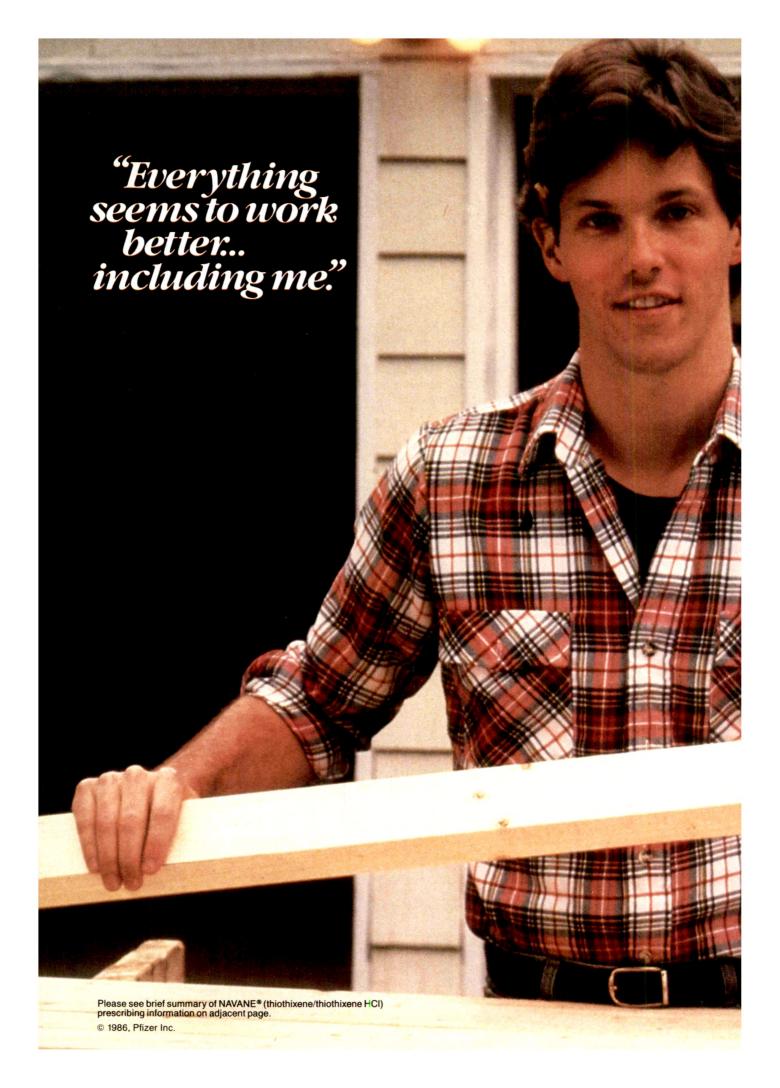
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#### **BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg (thiothixene hydrochloride) Concentrate: 5 mg/ml, intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose Contraindications: Navane (Iniothixene) is contraindicated in patients with circulatory Collapse, commons states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered. Warnings: Tardive Dyskinesia—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to the property of the property of

sible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, it neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic iliness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should

be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of lardive dyskinesia and its clinical detection, please refer to

the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to

date have not demonstrated any teratogenic effects. In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety

and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur

in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate ovulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

arropine or related orugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue cul-ture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum protactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered

tween currents auministration in tiese drugs and maininary union igenesis, are available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the butlock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothix-ene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotensi occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pre sure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixen These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence these changes is lower than that observed with some phenothiazines. The clinical significance of these changes in the clinical significance of the clini

is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Nave therapy. The incidence of sedation appears similar to that of the pierazine group of phenothiazines, but Ik than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted w

Navane. Seizures and paradoxical exacerbation of psycholic symptoms have occurred with Navane infrequent Hyperrellexia has been reported in infants delivered from mothers having received structurally related drug In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal floatementation.

autonimentes.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Magement of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptomay require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed reducing the dosage of Navane and/or administering an oral antiparkinson agent.

reducing the dosage of Navane ano/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some |
tients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be gree
in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patie
appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the long

appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tong tace, mouth or jaw (e.g., protrusior of tongue, pulfing of cheeks, puckering of mouth, chewing movemen Sometimes these may be accompanied by involuntary movements of extremities

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoin beta that been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If to rany other presentation of the syndrome is observed, the clinician should consider possible discontinuat of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transminase and alkaline phosphatase, usually transient, have been frequently experted is expected in the properties of significant profitmed cases of significant striphylable to Navare have be

frequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have be

Hematologic Effects: As is true with certain other psychotropic drups, leukopenia and leukocytosis, which

Hematologic Effects: As is the wint certain other psychrotopic drugs, leukopenia and leukocytosis, with usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated w agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Altergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been ported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, foliative dermatitis and contact dermatitis (in nursing personnel) have been reported with cert

Endocrine Disorders: Lactation, moderate breast enlargement and amenormea have occurred in a small penalage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomas hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increa

salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associa with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite a weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine there and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiaz derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of cough reflex. In others, the cause could not be determined nor could it be established that death was due

phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronic and severity of the condition. In general, small doses should be used initially and gradually increased to optimal effective level, based on patient response:

Some patients have been successfully maintained on once-a-day Navane therapy. Usage in children under 12 years of age is not recommended because safe conditions for its use have not b

established.

Navane Intramuscular Solution: Havane For Injection—When more rapid control and treatment of acute havior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nat of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or e

impossible. For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the us dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decrea depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum r ommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It r be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recomendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily indicated as subsequent interested to 15 mg days the condition of the official conditions of the oral days of the conditions of the oral days of the oral da

Navation Capsules, Navation Concentrate—In Influer Continuous, an influe due to a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is offective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gr

overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dyspha hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since volvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdose If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids a or vasoconstrictors.)

or vasconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pres agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the us pressor action of these agents and cause further lowering of the blood pressure. It CNS depression is present and specific therapy is indicated, recommended stimulants include amphi mine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. pic

toxin or pentylenetetrazed) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson dru.

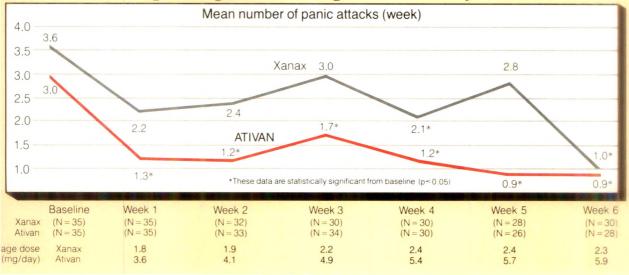
There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in p

nothiazine intoxication.



cumented icacy

#### Ativan® vs Xanax®† (alprazolam) in reduction of panic episodes during six-week study<sup>1</sup>



(lorazepam

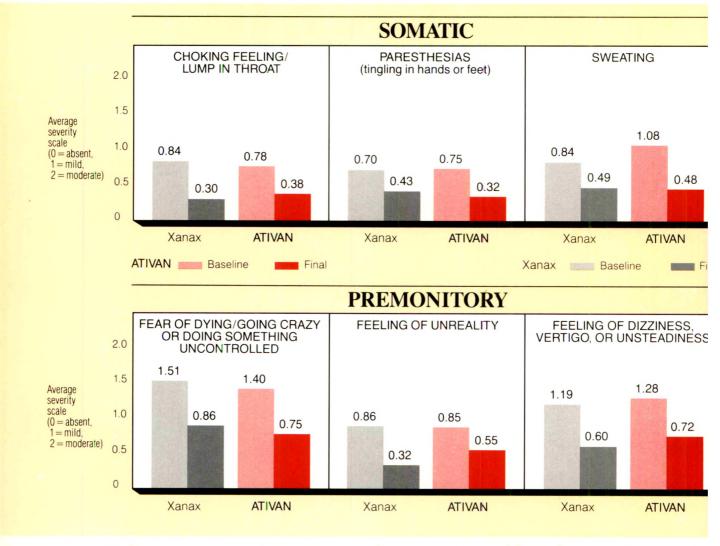
## Helps keep panic attacks under control

\*As defined in Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised). Used by permission of the American Psychiatric Association. †Xanax is a registered trademark of The Upjohn Company.

See last page for brief summary of prescribing information.

## Ativan<sup>®</sup> (lorazepam) effectively reduc

A multicenter, double-blind, six-week study compared Ativan<sup>®</sup> (N = 40) to Xanax (N = 37) in relieving symptoms of panic disorder as defined by DSM-III-R diagnostic criteria<sup>1,2</sup>



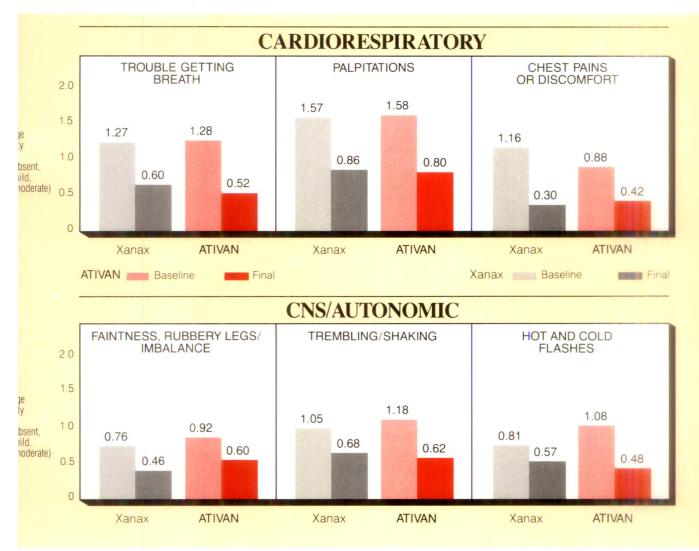
The panic attacks usually last minuinitially, are unexpected, i.e., they do no situation that almost always causes are attacks are not triggered by situations

### **UDY CONFIRMS:**

## najor symptoms of panic attacks

#### Efficacy equal to Xanax in reducing the symptoms of panic attacks

As compared to Xanax, Ativan\* demonstrated equivalent reduction in individual symptom severity<sup>1</sup>



nediately bativan's nediately bativan's (lorazepam) (lorazepam)

Helps keep panic attacks under control

## For relief of anxiety

## Prescribe Ativan®

#### Because:

Simple metabolism by conjugation, no active metabolites

Clearance is not significantly delayed by age, liver, or kidney dysfunction

Little likelihood of drug interactions with numerous, commonly prescribed medications

(All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)



#### Specify Ativan®-maintain the integrity of your prescription while assuring your patients' therapy

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Dispense as written
- Brand necessary
- May not substitute
- Medically necessary
- No substitutions
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment. with an anxiolytic

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle

Warnings: Not recommended in primary depressive disorders or psychoses As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants

vehicles, and of diminished tolerance for alcohol and other CNS depressants. Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for

suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to
avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any
antianxiety agent may result in symptoms like those being treated, anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual
precautions with impaired renal or hepatic function. Where gastrointestinal or carprecautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS. Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drugteated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiaze-poxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3.500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are discrientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

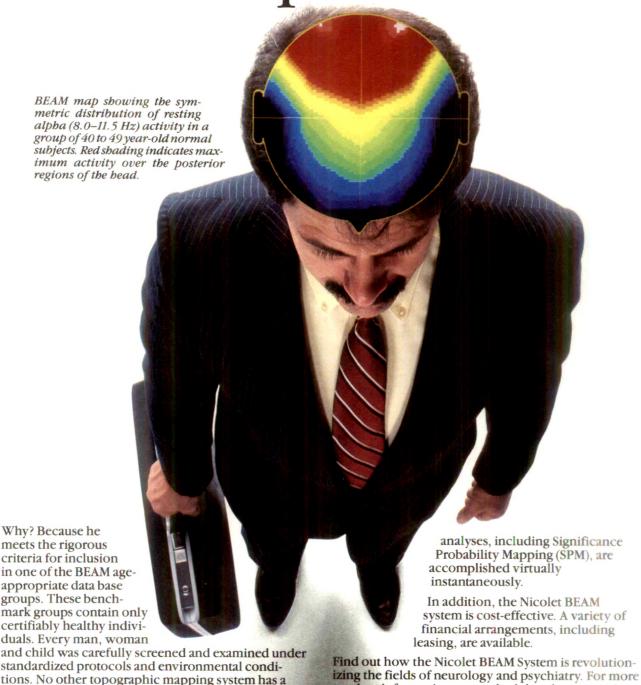
HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

References: 1. Data on file, Wyeth Laboratories. 2. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, ed 3 (revised). Washington. DC American Psychiatric Association, 1987.

The appearances of Ativan tablets are registered trademarks of Wyeth Laboratories.



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For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

#### **OCTOBER**

October 4–7, annual meeting, Southern Regional Conference on Mental Health Statistics, New Orleans. Contact Mr. John E. Bianconi, Chairperson, West Virginia Dept. of Health, Office of Behavioral Health Services, 1800 Washington St., East, Bldg. 3, Rm. 451, Charleston, WV 25305; 304-348-0627.

October 6–11, annual meeting, American School Health Association, Indianapolis. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 7–10, annual meeting, American Academy of Clinical Psychiatrists, Toronto. Contact Robert Budetti, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-460-2675.

October 8–11, annual meeting, American Medical Care and Review Association, Monterey, Calif. Contact Ronald A. Hurst, Executive Vice-President, 5410 Grosvenor Ln., Suite 210, Bethesda, MD 20814; 301-493-9552.

October 9–12, Vth Scientific Conference of the International Federation of Psychoanalytic Societies, New York. Contact Ann R. Turkel, M.D., Secretary-General of the IFPS, 350 Central Park West, New York, NY 10025; 212-831-3400.

October 11–16, annual meeting, American College of Surgeons, San Francisco. Contact C. Rollins Hanlon, M.D., F.A.C.S., Executive Director, 55 East Erie St., Chicago, IL 60610; 312-664-4050.

October 15–17, annual meeting, Canadian Association for Community Living, Washington, D.C. Contact Jacques Peletier, Executive Vice-President, Kinsmen Bldg., York University Campus, 4700 Keele St., Downsview, Ontario M3J 1P3, Canada; 416-661-9600.

October 15–17, annual conference, Canadian Group Psychotherapy Association, Banff, Alberta, Canada. Contact Dr. Edgardo Perez, Dept. of Psychiatry, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9, Canada.

October 15–17, annual meeting, National Association for Retarded Citizens, Washington, D.C. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue "J," Arlington, TX 76006; 817-640-0204.

October 15–18, annual meeting, American Academy of Psychiatry and the Law, Ottawa. Contact Ms. Kathy Smith, AAPL, 1211 Cathedral St., Baltimore, MD 21201; 301-539-0379.

October 17–19, annual meeting, Association of Mental Health Librarians, Boston. Contact Zing Jung, M.L.S., American Psychiatric Association Library, 1400 K St., N.W., Washington, DC 20005; 202-682-6057.

October 18–21, annual meeting, American Neurological Association, San Francisco. Contact Jan W. Kolehmainen, Executive Director, 2420 Pershing Rd., Kansas City, MO 64108; 816-474-5720.

October 18-22, annual meeting, American Public Health Association, New Orleans. Contact William H. McBeath, M.D., M.P.H., Executive Director, 1015 15th St., N.W., Washington, DC 20005; 202-789-5600.

October 18–22, annual meeting, World Medical Association, Inc., Madrid. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 33-50-40-75-75.

October 19–23, annual meeting, American Society for Therapeutic Radiology and Oncology, Boston. Contact John Ciccone, ASTRO, 1891 Preston White Dr., Reston, VA 22091; 703-648-8910.

October 19–25, annual meeting, World Federation for Mental Health, Cairo. Contact Eugene B. Brody, M.D., Secretary General, 1021 Prince St., Alexandria, VA 22314-2932; 703-684-7722.

October 20–22, Third International Conference on Rural Rehabilitation Technologies, Grand Forks, N.D. Contact Deb Gasal, ICCRT Headquarters, Office of Clinical Development, Box 8202, University Station, Grand Forks, ND 58202; 701-780-2495.

October 21-22, annual meeting, Institute of Medicine, National Academy of Sciences, Washington, D.C. Contact

(Continued on page A37)





The active metabolite of amitriptyline

## All the efficacy of amitriptyline and a favorable side effect profile

Because of anticholinergic activity, PAMELOR (nortriptyline HCI) should be used with caution in patients who have glaucoma or a history of urinary retention.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAQ) inhibitor, since hyperpyrelic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations: MAQ inhibitors should be discontinued for at least two weeks before treatment with Pamelor\* (nortriptyline HCI) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCI), cross-sensitivity with other dibenzazepines is a possibility. 3) The acule recovery period after myocardial infarction

acule recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children – Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established

Precautions: Use inschizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimelidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possibile, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment, in this regard, it is important that the least possible quantity of drug be dispensed any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: Cardiovascular—Hypotension, hypertension, tachycardia, palpitation myocardial infarction, arrhythmias, heart block, stroke. Psychiatric—Conflusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania, exacerbation of psychosis. Neurologic—Numbness, tingling, pares-

thesias of extremities; incoordination, alaxia, tremors, peripheral neuropathy; extrapyramidal symptoms, seizures, alleration in EEG patterns; tinnitus, Anticholinergic—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis constipation, paralytic ileus, urinary relention, delayed micturition, dilation of the urinary tract. Allergic—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and longue), drug lever, cross-sensitivity with other tricyclic drugs. Hematologic—Bonemarrow depression, including agranulocytosis; eosinophilia, purpura, thrombocytopenia. Gastrointestinal—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. Endocrine—Gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence; testicular swelling, elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antiduretic horrmone) secretion. Other—Jaundice (simulating obstructive), altered liver function; weight gain or loss, perspiration. Itushing, urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue; headache; parolid swelling, alopecia. Withdrawal Symptoms—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia. ECG evidence of impaired conduction, shock, congestive heart failure, stupp, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antitote is known, general supportive measures are indicated, with gastric lavage.

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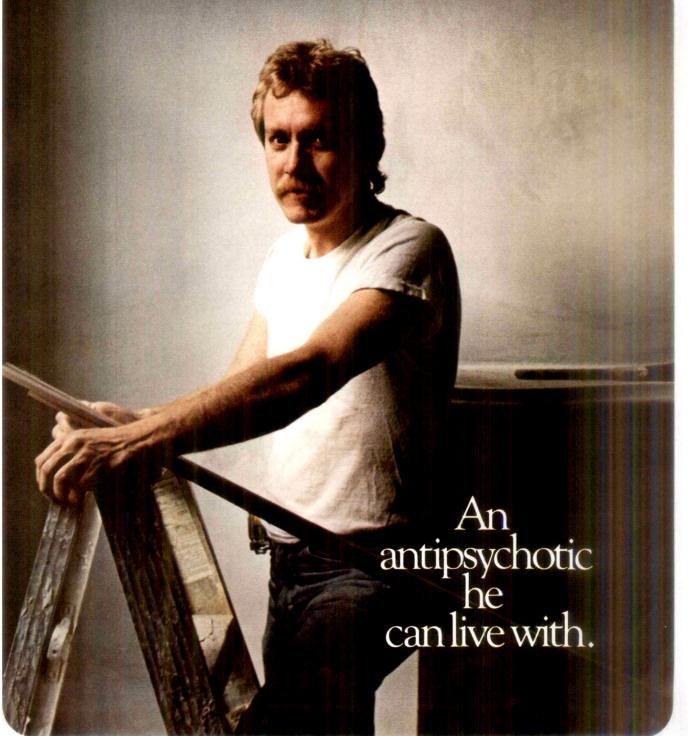
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# (mesoricazine) as the besylate MICONCENTRATE/TABLETS (R)



Please see following page for brief summary of prescribing information

## as the besylate R

(mesoridazine) besylate tablets USP (mesoridazine) besylate injection USP (mesoridazine) besylate oral solution USP

0000

Tablets: 10, 25, 50 and 100 mg

Concentrate: 25 mg/ml

Injectable: 1 ml (25 mg)

#### **Brief Summary of Prescribing Information**

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or cornatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersen-

cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug. 
Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

toses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions). Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

detection, please refer to the sections on Information for Patients and Adverse Reactions). Where patients are participating in activities requiring complete mental alertness (g. g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen white receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Issue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been rep

reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos)

have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have

been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have

been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bilid T or a U wave have been observed ir some patients receiving the phenothiazine tranquilizers, including Serentila (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia. Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The sallent features of this syndrome are described in the Warnings section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the longue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely. The syndrome may become clin cally recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced penodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Relention, incontinence.

Others: Hyperprexia. Behavioral effects suggestive of a paracoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a p

erythematosus-like syndrome. 
#\text{Mow Supplied:}

Serentil\* Tablets, for oral administration: 10 mg, 25 mg, 50 mg and 100 mg mesoridazine (as the besylate). Bottles of 100. 
Serentil\* Ampuls, for intramuscular adm.nistration: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20 and 100. 
Serentil\* Concentrate, for oral administration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume. 
Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 
bottles, with an accompanying cropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

SE-BPI-9/85



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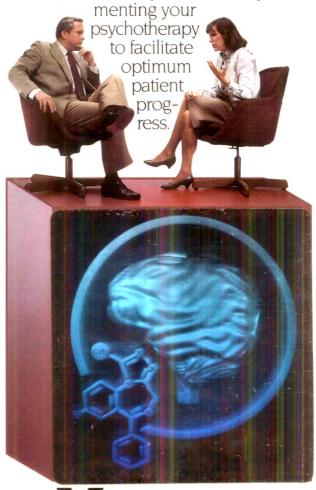
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## A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.

The incorporation of a triazolo ring to the basic benzodiazepine structure clearly differentiates Xanax from other benzodiazepines.

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### A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.



#### XANAX\* Tablets (alprazolam) @

#### CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

#### WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

#### **PRECAUTIONS**

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. Drug/ Laboratory Test Interactions: No consistent pattern for a specific drug or specific test. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic potential or impairment of fertility in rats. Pregnancy: See Warnings. Nonteratogenic Effects: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. Labor and Delivery: No established use. Nursing Mothers: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

#### ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness. syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/ palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor. Cutaneous: Dermatitis/allergy. Other side effects: Nasal congestion,

weight gain, and weight loss. In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia,

dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

#### **DRUG ABUSE AND DEPENDENCE**

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

> B-4-S J-6338 January 1987

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## Breaking away

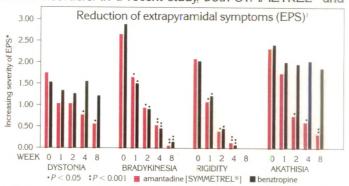


### rom the clutches of EPS

#### Effective control of extrapyramidal symptoms (EPS)

SYMMETREL® (amantadine HCl) has been proven clearly effective in controlling a broad range of extrapyramidal movement disorders. In a recent study, both SYMMETREL® and

benztropine "were equally effective in treating druginduced parkinsonism; however, amantadine [SYMMETREL®] proved somewhat more effective in reducing akathisia and recurrent dystonia."



\*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p 42

#### Fewer side effects than anticholinergics

Dramatically differentiating SYMMETREL® from anticholinergics is its favorable side effect profile. With fewer anticholinergic side effects, SYMMETREL® affords patients greater com-

fort—encouraging compliance with their antipsychotic regimen. SYMMETREL® is not metabolized and is mainly excreted in the urine. Care should be taken, however, in patients with renal impairment. SYMMETREL®. The more rational and safer¹ therapeutic choice in the control of EPS.

Incidence of anticholinergic side effects				
	% patients taking amantadine	% patients taking benztropine		
Dry mouth	7.4	41.6		
Blurred vision	2.6	26.5		
Nasal congestion	2.5	18.2		
Constipation	1.8	21.4		
Urinary hesitancy	1.3	7.1		

—adapted from Borison and Diamond, p 431



Please see following page for brief summary of prescribing information







BRIEF SUMMARY OF PRESCRIBING INFORMATION

BRIEF SUMMARY OF PRESCRIBING INFORMATION INDICATIONS AND USAGE: Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions: SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa. ()-3-(3. 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL.

receiving SYMMETREL.
Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring

of vision should be cautioned against driving or working in situations where alertness

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontin PHECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be

exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are: depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety, irritability, anorexia, nausea, and constipation, ataxia and disziness (lightheadedness): livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

daily, if necessary,

one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit. When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

Dosage for Drug-Induced Extrapyramidal Reactions: Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

6043-15BSP/Rev. Oct. 1984

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702

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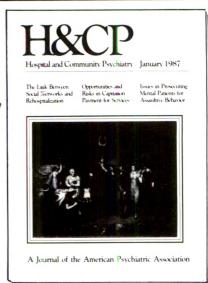
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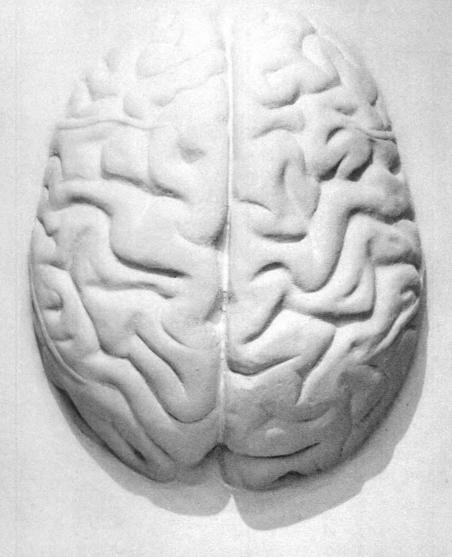
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# BRAINS



he human mind, a busy, complex abyrinth of thought, perception and calculation. By definition, the ource of cerebration.

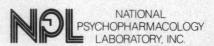
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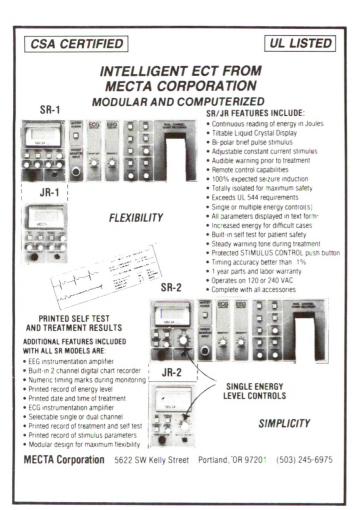
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product information, a summary of which follows:
Indications: Management of anxiety disorders;
short-term relief of anxiety symptoms, acute alcohol
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and anxiety. Usually not required for anxiety or
tension associated with stress of everyday life. Efficacy beyond four months not established by
systematic clinical studies. Periodic reassessment of
therapy recommended.

Contraindications: Known hypersensitivity to the drug.

Wamings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals ar those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they inlend to or do become pregnant.

**Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmaco logic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dystunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. Oral—Adults: Mild and moderate anxiety disorders and symptoms, 5 or 10 mg f.i.d. or q.i.d.: severe states, 20 or 25 mgt.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See

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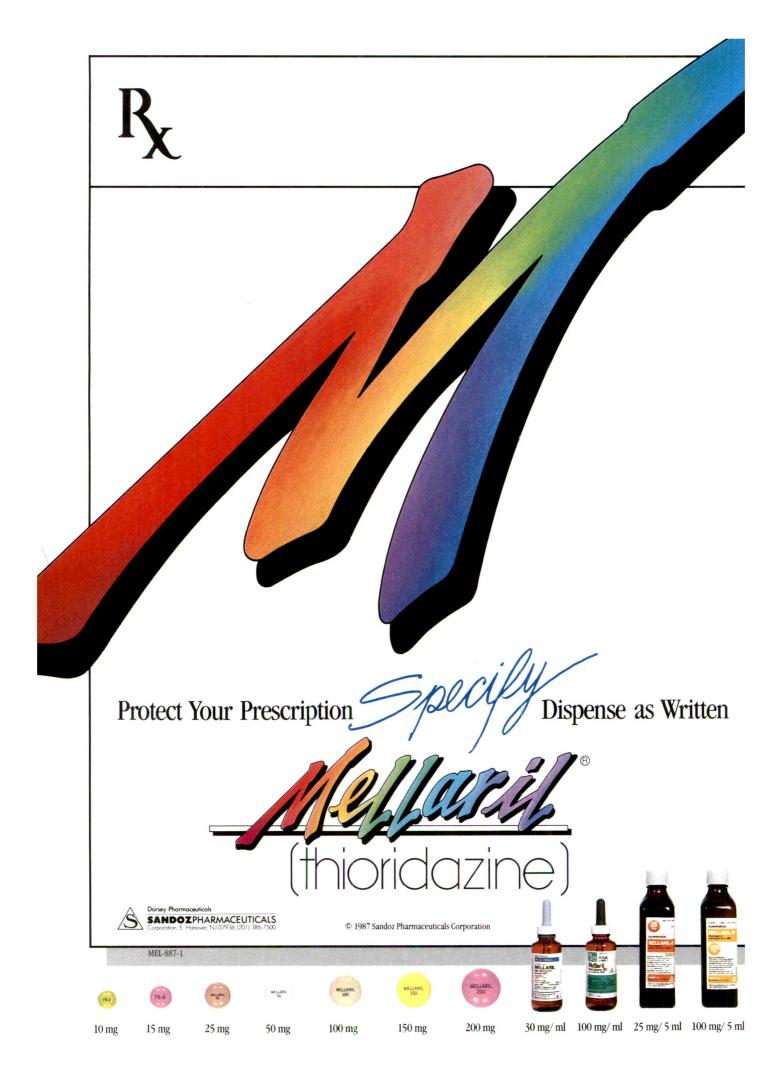






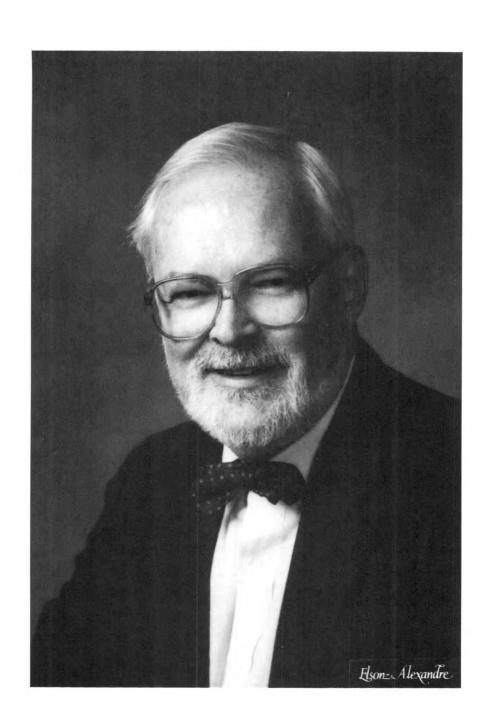
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# Presidential Address: Psychiatry in Medicine: Medicine in Psychiatry

Robert O. Pasnau, M.D.

The integration of psychiatry and medicine has been a goal of American psychiatry from the very beginning. The earliest attempt to coordinate psychiatric and medical care and teaching in America was undertaken by Benjamin Rush, who is known as the most famous American physician of the eighteenth century. During the 30 years that he served as physician to the Pennsylvania Hospital in Philadelphia and Professor of Medicine at the University of Pennsylvania, he stressed in his lectures the unity of body and mind, emphasizing the importance of the knowledge of mental functions on the teaching and practice of medicine. His textbook of psychiatry, published in 1812 (1), was the first American medical textbook. It influenced generations of American physicians.

#### THE ROLE OF PSYCHIATRY IN MEDICINE

I have spent most of my professional life involved in the interface of psychiatry and medicine. This presidential theme has great personal meaning and significance for me. During the past 25 years I have witnessed the role of psychiatry in medicine expanding in clinical, educational, and research areas, and in each of the years, new clinical challenges have arisen. I have watched the development of consultation-liaison psychiatry during the 1960s and 1970s, the contributions that have been made in the treatment of patients with cancer, heart disease, renal failure, brain injury and dysfunction, and, most recently, organ transplanta-

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tion, Alzheimer's disease, and acquired immunodeficiency syndrome (AIDS). I have seen child psychiatrists being called upon to work more closely with children and their families in pediatric wards, newborn intensive care settings, burn units, cancer services, and organ transplantation units. I have witnessed older people with terminal illnesses living longer and requiring continued psychiatric care as their lives are extended by improved medical treatments. I have also worked closely at the interface of medical education with the primary care physicians who provide over one-half of all mental health services to patients. And there is growing awareness on the part of our medical colleagues of the need for up-to-date and relevant psychiatric education as part of their continuing medical education.

During the past 25 years, I have watched the role of psychiatry in organized medicine continue to expand. Psychiatrists are becoming more involved with their national and state medical associations, specialty boards, and other specialty societies. As hospital staff organizations have assumed a more important and significant role in the development of standards, psychiatrists have played increasingly important and valuable roles in their hospital staff organizations. With increased awareness of physician impairment, the participation of psychiatrists on impaired physician committees is imperative. So too is the role of psychiatric consultants in general hospitals. As Lipowski has recently written (2), the most far-reaching development in the interface of psychiatry and medicine in this century has been the formation of general hospital psychiatric units. These have helped to reduce the isolation of psychiatry and the mentally ill from the general health care system, stimulated research at the interface, and enhanced the quality of patient care. "Both psychiatry and medicine have been enriched as a result" (2). I have seen that as psychiatrists have become more active with their colleagues in the rest of

medicine through these activities, they have indeed become the "goodwill ambassadors" for psychiatry in medicine.

I have also seen the role of medicine in psychiatry undergo equally impressive expansion over the past 25 years. Scientific advances in psychiatry have continued to emphasize psychiatric research, and recent developments employing new biological technologies are finding important applications to clinical psychiatry. Equally impressive advances in psychopharmacology and somatic therapies, psychotherapy research based upon outcome studies, computer-assisted assessment and evaluation, and improved nosology continue to improve the reputation of psychiatry with our medical colleagues. It is not surprising to me that more medical students than ever are seeking to enter psychiatric careers.

#### THE NEED FOR CREATIVE PROBLEM SOLVING

Today, we are at a crossroads. The firm identity of psychiatry as a specialty of medicine and its improved image and viability provide promise and opportunity. But many forces are making an impact on our profession and our commitment to provide quality medical care. A top priority for all of medicine is the provision of quality care in the face of severe fiscal constraint and cutbacks. Perhaps for the first time in recent history, we are faced with the crisis of underutilization.

Underutilization of medical services will not be cost effective. Rather, it may directly *increase* health costs through expensive readmissions or prolonged treatment of preventable complications. Further, the indirect costs to society are equally underestimated. The problems of increased absenteeism, decreased employee morale, and declining productivity, as well as future increased health care costs due to undertreatment of preventable conditions, could prove to be the greatest tragedy of our current period.

Will the American people stand for 5-year waiting lists for elective surgery, outpatient treatment of stroke and serious heart disease, and premature discharge from intensive care units and psychiatric hospitals? Sammons is convinced that quality of care can only depend on whether *physicians* take a strong leadership role in defining and determining the appropriate measures of quality care (J.H. Sammons, "An Overview of Quality Issues," unpublished paper, 1987).

Perhaps now more than ever before we need to join in coalitions with consumer groups, labor unions, and patient and family organizations to educate and explain to industry and government the hazardous road of rationing and curtailment of all health services. We have been particularly successful in learning how to work with other advocacy groups for the mentally ill, including the National Alliance for the Mentally Ill (NAMI), the National Mental Health Association, the American Mental Health Fund, and the National Mental Health Consumers Association. We have even

progressed to testifying jointly. For example, a NAMI witness testified on behalf of APA concerning the critical issue of catastrophic health insurance coverage of mental illness. These efforts do far more than lift the shroud of stigma; they greatly contribute to enhanced awareness of the need for quality of care. The physical and psychiatric needs of patients deserve the most that we and our medical colleagues can marshal. Consultation and referral, and accessibility for these activities, require our attention.

Beigel, in an eloquent address entitled "Where is the Yellow Brick Road?", warned about what we must not do (A. Beigel, unpublished paper, 1987). We must not continue to play the same old music like the ballroom musicians on the Titanic. We must not keep thinking that current medical economics is unfair because nobody told us that things would be like this when we chose to be physicians. We must not continue to view adverse selection as an attack on our profession rather than an economically driven process. And we must not continue to hope that things will change if we only continue to talk cogently and persuasively to ourselves about the dangers of these current events.

Medicine must always react to the prevailing currents in the society in which it is practiced. Medical leaders must seize the opportunities for creative and innovative problem solving. In his address to the Massachusetts Medical Society in May 1860, Dr. Oliver Wendell Holmes, father of the famous jurist, wrote the following:

The truth is that medicine, professedly founded on observation, is as sensitive to outside influences, political, religious, philosophical, imaginative, as is the barometer to the changes of atmospheric density. Theoretically it ought to go on its own straightforward inductive path, without regard to changes of government or to fluctuations of public opinion. But . . . [there is] . . . a closer relation between the Medical Sciences and the conditions of Society and the general thought of the time, than would at first be suspected (3).

#### HIGHLIGHTS OF OUR ACHIEVEMENTS

Last year in response to President Nadelson's poignant question, "Who cares for patients?" (4), I made a call for action to encourage more of our members to take an active role in solving the problems involved in remedicalization. I urged us to mobilize, joining with the rest of medicine in declaring that the United States is facing a crisis in medical practice. I said, "Our voice can be a mighty one when it is joined with the rest of medicine" (5). The results in the past year have been impressive. By collaborating with our medical colleagues, we have taken some major steps forward. Let me highlight some of the achievements.

Perhaps the greatest improvement has occurred in our participation with the AMA and its House of Delegates. In strengthening our already excellent working relationship with AMA, its House of Dele-

gates, during the AMA meeting last December, resoundingly supported all of those issues which were so important to psychiatrists and their patients. Among others, AMA endorsed a new policy supporting the equitable reimbursement for psychiatric illness and opposing limitation of Medicare reimbursement for the mentally ill; a study of the special health insurance problems posed by psychiatric illness, with proposed solutions for adequate coverage; the selection of psychiatrists for membership on two of AMA's important councils, the Council on Legislation and the Council on Scientific Affairs; and the selection of APA nominees for prestigious scientific awards. The recent seating of the American Academy of Child and Adolescent Psychiatry in the AMA House of Delegates increased psychiatry's voice in AMA house deliberations. Recommendations for nondiscrimination in coverage of mental illness in health insurance and increased federal funding in both basic and applied research by the various health institutes and the Veterans Administration were also strongly supported by the AMA House of Delegates.

Our relationship with the rest of medicine, however, is much more than a relationship with organized medicine. It is in the day-to-day contact with our medical colleagues, the public, the families of our patients, and our patients that the battle to overcome the stigmatization of psychiatric disorders must continue to take place. During my lifetime I have seen a change in the way that psychiatrists and psychiatric patients have been viewed. In my internship class of 16, none of the four of us who were planning careers in psychiatry dared to inform the selection committee of our interest, for fear that we would not get our coveted positions. Many of us suffered demeaning jokes from our fellow residents in other medical specialties. I shall never forget the professor of surgery whose rounds I attended while still a resident. Upon learning that I was a psychiatric resident, he glowered at me and muttered, "What a hell of a waste of a medical education." While such outrageous stereotyping still occurs, there has been a profound change in the degree and valence of such attitudes.

Partly in response to such historical discrimination and partly out of a challenge from then Public Affairs Chair Paul Fink, I was stimulated to write an article outlining some rules of etiquette for psychiatrists (6). This tongue-in-cheek effort to heighten awareness of our own contribution to our interdisciplinary problems resulted in a cartoon-illustrated personal calendar which was premiered at the recent Public Affairs

Institute held in January in Tucson.

Beginning with the Mental Illness Awareness week, a nationwide public education campaign orchestrated by APA to improve public understanding of mental illness and its psychiatric treatment has been the year-long focus of the APA Division of Public Affairs. At the Tucson Institute, over 250 representatives from the district branches attended a meeting that focused on ways in which individual psychiatrists can advance the interests and image of psychiatry to our nonpsychiatrist physician colleagues as a part of the Physicians Awareness Campaign. We began that campaign by encouraging our members to become involved with other mental health organizations.

Our national marketing project has also had an impact on our image. In just 2 years, the accomplishments have included developing annual recommendations for district branch staff roles in marketing; presenting data showing the cost effectiveness of providing psychiatric treatment; educating our membership on current mental health economics, with practical applications for practice development; and, most importantly, bridging the gap in insurance decision making by establishing productive dialogues with those in industry who purchase the health benefit packages for their employees. We have made an impressive beginning, and we are now planning new strategies for the coming decade.

I am particularly pleased by our liaison efforts with the 99th Congress. Through the hard work of the Joint Commission on Government Relations and the Division of Government Relations, APA was instrumental in defeating legislation that would have deleted Medicare's funding support for the training of child psychiatrists, mandating a report to Congress on health maintenance organization arrangements that improperly limit medically necessary services, and requiring that the Omnibus War Against Drug Abuse Bill protect the integrity of scientific peer review from "politicalization." We have been successful in promoting a "Sense of Congress" resolution that Federal Employees Health Benefits Program carriers "provide adequate benefits on mental illness, alcoholism and drug addition," including coverage of inpatient and outpatient treatment, as well as

catastrophic protection benefits.

We have lobbied successfully for a \$100 million increase over budget for mental health research and \$15 million for clinical training and for amending the Vocational Rehabilitation Act to ensure attention to the chronically mentally ill. The major psychiatric issues for us in working with the 100th Congress include encouraging Congress to pass our Mental Illness Awareness Week Resolution and supporting the "Medicare Mental Illness Non-Discrimination Act" in the House and Senate. We have joined in a broad coalition of mental health professionals and patient groups to assure that catastrophic insurance legislation includes coverage for the mentally ill and will continue our APA-led coalition efforts to increase funding for research, training, and service in substance abuse and mental health, as well as efforts to increase coverage for mental illness. I have just learned that we broke a 20-year tradition of tragic discrimination during my presidential year. The House Ways and Means Committee has just approved a bill to increase ourpatient psychiatric coverage under Medicare. We now begin our first "nondiscriminatory" legislative journey. All of these initiatives are related to the theme of psychiatry in medicine, to our being viewed as an integral part of medicine and a vital part of the health care system. Psychiatry in medicine means that we continue to view as our responsibility playing an active role in medicine's struggle for providing high-quality medical care for all of our patients.

This leads me to comment on our relationships with psychology, social work, and nursing. In my recent address to the Board of Directors of the National Association of Social Workers, I acknowledged a possible misinterpretation of the term "remedicalization." During our present remedicalization we cannot, on behalf of our patients, turn our backs on colleagues in allied mental health disciplines. Through our participation with psychology, social work, and nursing organizations in the Joint Commission on Interprofessional Affairs, we have witnessed the growth of more constructive interprofessional relationships during the past year. Our meetings allow for serious face-to-face discussion of current trends and issues for each of the professions and foster better mutual understanding.

A discussion document of the Joint Commission on Interprofessional Affairs, Guidelines for Interprofessional Relationships in the Mental Health Field (7), has been circulated to national and district branch leadership. In no way does it override any official APA policy. All of the professions recognize the potential for benefit through collaboration, both to the professions and to our patients. We believe that when spokespersons of our four professions publicly disparage the competency and ethics of the others' professions, all of us are injured. We must do all we can to eliminate unnecessary tension between us while we continue to articulate our special areas of competency. This is sometimes a delicate balance.

Increasingly, we see examples of effective state coalition work for moving mental health appropriations or securing mandated benefit legislation. Such activities of the Joint Commission on Interprofessional Affairs have become a vital element in the process of many state-level actions in which we will be involved, notwithstanding recurrent and often severe tensions among us that arise from time to time. Some of our state organizations have been more successful than our national ones. We shall learn and profit from the experiences of the child psychiatrists who have proved that patients benefit most when we work together.

International affairs continue to play an important role in our organization. During the past 2 years I have visited 18 countries on six continents, met with psychiatrists, visited psychiatric centers and academic departments, and addressed international and national psychiatric meetings. Let there be no doubt about the esteem in which the world, including the Soviet Union, holds American medicine and American psychiatry. There is particular respect paid to APA and its activities, witnessed by the number of outstanding international leaders attending this meeting.

We have also made many important advances in our international affairs, including sponsoring a joint meeting with the African Psychiatric Association and

the Black Psychiatrists of America in Kenya to facilitate the sharing of scientific knowledge and cultural understanding; sponsoring a conference on "Living Abroad: Adjustments and Crises" with the American Bar Association and the U.S. State Department; and coordinating an International Education Project involving foreign psychiatrists who will come to the United States to study specific areas of psychiatry, returning to teach this knowledge in their countries.

We will continue to speak out against the abuse of psychiatry and psychiatrists wherever it exists. I believe that the release of our courageous colleague, Dr. Anatoly Koryagin, from forced labor to emigration to Switzerland is proof that our policy has been correct. We have expressed our opposition to the United Nations report on detention on the grounds of mental ill health or mental disorder (the so-called "Daes Report") (8), which has a strong antipsychiatry slant, by objecting to the distribution of this report. We are awaiting the deliberations of the United Nations Human Rights Commission and are prepared to respond.

It has sometimes been difficult to explain why I consider international relations to be a significant part of psychiatry's relationship to medicine. It seems to me that the role and status of psychiatry around the world affect the image of psychiatry in the United States and its stigmatization of psychiatrists and patients with mental illness. It is important to psychiatry and all of medicine that no physicians be abused and that no specialty be exploited. I believe American medicine and American psychiatry have played and should continue to play a leading role in the development of quality medical care throughout the world. We should stand ready to assist our colleagues wherever they may be practicing and in whatever repressive or primitive conditions they may serve. It is to our credit that APA has been so responsive to the requests and needs of our associates around the world. What I have learned is that psychiatrists all over the world recognize the importance of improving the relations between psychiatry and medicine in their countries.

But national and internal issues are equally important to our remedicalization. I am pleased that APA has developed position statements on discrimination related to AIDS and the human immunodeficiency virus (HIV) that highlight the responsibilities of psychiatrists to educate themselves, their patients, and communities with regard to the neuropsychiatric and psychosocial aspects of HIV disease and to reduce the anxiety and unjustified fears about AIDS-related issues. I applaud the publication of the recent task force report "Changing Family Patterns in the United States" (9), a report that should provide a perspective to anticipate needs and strengths to families and to make policy planning more effective.

Last year, I called attention to several internal professional concerns requiring resolution. We indeed have made good progress toward solving many of them. The first was professional liability and tort reform. We have come through our own professional

liability crisis by establishing the Psychiatrists' Mutual, an insurance company owned and operated by APA. One-third of our membership is insured by this company, which offers competitive rates and occurrence coverage. It appears that other medical specialties may be interested in the type of arrangement offered by APA's insurance company. Tort reform is progressing slowly but steadily.

Last year I indicated that the development of treatment standards was one of the top priorities for all of medicine and may be the major quality-of-care issue for the 1980s. While we are still a long way from accomplishing this goal, more members than ever before recognize the need for the gradual development of treatment standards in psychiatry. Further, this must be done by psychiatrists, *not* by nameless bureaucrats in government or industry.

At the Institute for Hospital and Community Psychiatry last October, I noted the controversy surrounding the development of the report of the APA Task Force on Treatments of Psychiatric Disorders. Those of us who have read it are impressed at the breadth of the subjects, the flexibility of the approaches, and the scholarship of the authors (10). A major hurdle was overcome in December when the Board of Trustees agreed to publish this work as a task force report, rather than as an official position statement of APA. The Assembly Executive Committee further worked at conflict resolution by agreeing to make the draft chapters available to the areas and district branches for review and by working together with the Board of Trustees to iron out the final unresolved issues. Thus an important first step has been taken in a process most difficult for psychiatrists to attempt, but one that will have important implications in the years

I am pleased that DSM-III-R has been published and made available at the 1987 annual meeting. Although the approval process was stormy and controversial, I am pleased that it resulted in several reasonable and sensitive compromises that made publication possible in time for this meeting. Committees are beginning to think about DSM-IV and what the future holds for scientific nosology, not only for us but also for each of the clinical sciences in medicine. I believe we must align the scientific advances in basic neurobiology, neuroscience, and genetics with the diagnosis of patients with psychiatric disorders. The task is no different for nosology in all of medicine, where molecular, biological, and clinical epidemiological studies increasingly recognize new subtypes of disease.

It is exciting to contemplate what future lies in store for psychiatry. The future of any field depends on its research, and advances in neurobiology and neuroscience as they affect the diagnosis of treatment of patients with psychiatric disorders show great promise. Pardes has recently described the euphoria and, at times, apprehension that psychiatrists feel about the developments in neuroscience (11). In the past decade the pace has rapidly increased, and pioneering meth-

ods of study have been developed. Among these are brain electrical activity mapping, positron emission tomography, and magnetic resonance imagery. The applications of these techniques to patients with Alzheimer's disease and schizophrenia put psychiatry on the cutting edge of the future, beginning to unravel the mysteries of the brain (11).

At the same time, clinical psychiatric research has undergone an evolution. An example is found in epidemiological research using techniques for assessing the prevalence of psychiatric disorders based upon sharpened subcategories of psychiatric disorders found in *DSM-III*. Research in psychopharmacology continues, with new findings published at a dizzying pace about the use of different categories of medications in mania and schizophrenia. Increasingly efficacious psychotherapeutic and social skills training has been useful for a wide variety of patients.

#### **CONCLUSIONS**

Many challenges lie ahead. The theme that President Pollock has adopted for the next year will provide an opportunity to explore these areas. One of the things we must improve is how we explain what psychiatrists do, what psychiatry is, and what our patients can expect from treatment. To ensure the future of our specialty, psychiatry must be defined as the specialty that diagnoses, treats, and studies disturbances of mental processes. These disturbances may be caused by organic dysfunctions in the brain (structural or biochemical), biopsychosocial or environmental stresses, developmental processes, or often by all of these factors. As my year as your President draws to an end, as I have seen the energies of our organization respond, resolve conflicts, and anticipate necessary affiliations and coalitions, I am more certain than ever that we can find ways of responding intelligently to these current challenges. Let us look ahead to the future and see our challenges as opportunities.

We must continue to provide high-quality care in accordance with our ethical standards while we find ways to provide services that are more efficient, more effective, and maybe even more economical. This is a new era, and we must adopt a new attitude.

We must persist in our great efforts at the interface of psychiatry and medicine. We must continue our public relations activities, which strive to improve the image of psychiatry and to eliminate the stigma of psychiatric illness. We must press our liaison with the rest of medicine and the AMA, maintain our efforts at local and state levels, and remain as the public relations agents for our profession with our medical colleagues. We must persevere in our efforts, particularly at the state level, with allied mental health professionals. As we strive to be fair, we must insist on being treated fairly in public and legislative forums. We must continue to advocate for psychiatry and psychiatrists on an international basis and to speak out

against the abuse of medicine and psychiatry wherever it occurs. We must heighten our efforts to keep our organization strong, effective, and cohesive and to deal with our internal problems and anxieties in a way that does not undermine public confidence. If our profession can retain its strength and vitality, we in turn will strengthen and vitalize all of medicine. And then all of us—physicians, patients, and the public—will be the winners.

#### REFERENCES

- Rush B: Medical Inquiries and Observations Upon Diseases of the Mind. Philadelphia, Kimber and Richardson, 1812
- Lipowski ZJ: The interface of psychiatry and medicine: towards integrated health care. Can J Psychiatry (in press)
- 3. Holmes OW: Currents and counter currents in medical science in Medical Essays. Boston, Houghton Miflin, 1889
- 4. Nadelson CC: Presidential address: health care directions: who

- cares for patients? Am J Psychiatry 1986; 143:949-955
- Pasnau RO: Response to the presidential address: health care crisis: a campaign for action. Am J Psychiatry 1986; 143:955– 959
- Pasnau RO: Ten commandments of medical etiquette for psychiatrists. Psychosomatics 1985; 26:128–132
- Joint Commission on Interprofessional Affairs: Guidelines for Interprofessional Relationships in the Mental Health Field. Washington, DC, American Psychiatric Association, 1986
- Daes EA for the Sub-Commission on Prevention of Discrimination and Protection of Minorities of the United Nations Commission on Human Rights: Principles, Guidelines and Guarantees for the Protection of Persons Detained on the Grounds of Mental Ill-Health or Suffering from Mental Disorder. New York, United Nations, 1986
- American Psychiatric Association Task Force 25: Changing Family Patterns in the United States. Washington, DC, APA, 1986
- Pasnau RO: The remedicalization of psychiatry. Hosp Community Psychiatry 1987; 38:145–151
- 11. Pardes H: Neuroscience and psychiatry: marriage or coexistence? Am J Psychiatry 1986; 143:1205-1212

#### Response to the Presidential Address: Opportunities and Challenges That Confront Medicine and Its Specialties, With Special Reference to Psychiatry

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I t is a pleasure to welcome you to Chicago—our home town. This special occasion is a reunion. Our President, Dr. Robert Pasnau, was a medical student in Chicago, and I was one of his first teachers of psychiatry. Dr. George Tarjan worked in Illinois in the early years of his career in the United States. Dr. Harold Visotsky was at the University of Illinois, where we met 40 years ago, and I wrote letters of reference for him when he applied for residencies. Dr. Melvin Sabshin, our illustrious Medical Director, was in a class I moderated on research methodology at the Chicago Institute for Psychoanalysis, and later I was a

professor in his department at the University of Illinois. This is truly a coming together.

The theme I have chosen for my Presidential year is "Opportunities and Challenges for Psychiatrists and Psychiatry: 1988–2000." After I had decided on this focus, I came across a statement by Dr. William Menninger, a former President of APA and a graduate of the Chicago Institute for Psychoanalysis, that caught what I had in mind. Dr. Menninger wrote:

Although most professional people make their living by the use of intelligence, which may or may not be supplemented by the toil of their hands and the sweat of their brow, everyone makes his life through the emotions—through loves and hates, faith and hope, jubilations and disappointments. They are the vital part of life. We continuously react emotionally to the people and the things about us. Life is a flowing stream of opportunities, challenges, and problems which demand that, insofar as our capacity and our emotional response permit, we adjust and readjust to them. . . . Life—whatever your job—is a continuous growing process. (1, pp. 18–19)

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There are many areas of challenge that tie in with the theme of this meeting and the next one, giving us opportunities for thought, reflection, and action. In conjunction with President Pasnau's theme, it is important to emphasize that what affects medicine affects psychiatry. However, what affects psychiatry does not always affect medicine. In a recent report, Cohen (2) noted that there are some 250 million people in the world who are severely mentally ill. Roughly 1% of any population turns out to be schizophrenic and an additional 27% suffers severe depression. There are caring psychiatrists in most countries. The relationships among disease, the physician, and the patient are crucial for all of medicine. In psychiatry the varied transferences, the joint voyage of discovering their relationship, and the emphasis on experiencing make our discipline unique.

#### NATURE OF A PROFESSION

Let me turn to the question of what a profession is, as contrasted with service delivery. The word "profession" has a dual meaning. It is a species of a generic concept, namely, "occupation," and it is an avowal or promise. Bierstadt (3) asks whether the avowal or promise has been fulfilled: Does the professional do what he or she promises to do? What are the norms of the profession? What self-regulatory processes guarantee the competence of members of the profession? What are the standards of performance and how do we assess whether or not they are met? "A professional is a specialist by definition, but the more he specializes in the pursuit of his profession the more he may be induced to sacrifice the larger point of view and retreat, in turn, from the highest of ethical standards" (3, p. viii).

Eliot Freidson, one of the pioneers in the sociological study of the profession of medicine, has written extensively on the occupational organization of physicians and how it is distinct from the knowledge-skill base of the profession. Freidson finds it "useful to think of a profession as an occupation which has assumed a dominant position in a division of labor, so that it gains control over the determination of the substance of its own work" (4, p. xvii). He further notes that "unlike most occupations, it [medicine] is autonomous or self-directing. The occupation sustains this special status by its persuasive profession and the extraordinary trustworthiness of its members. The trustworthiness it professes naturally includes ethicality and also knowledgeable skill" (4, p. xvii). Two problems quickly present themselves: how has the profession's self-direction or autonomy been developed, organized, and maintained; and how does one understand the relationship of the profession's knowledge and procedures to the professional organization and to the lay world? Although Freidson wrote about this almost 15 years ago, the current relevance is obvious and applies not only to the profession of medicine but to its subdivisions, the specialties and subspecialties.

Medicine today "has developed into a very complex division of labor, organizing an increasingly large number of technical and service workers around its central task of diagnosing and managing the ills of mankind" (4, p. xviii). Bittker (5) has updated the issues and challenges in his paper "The Industrialization of American Psychiatry." He notes that psychiatry will be transformed into an industry in which prospective payment, automation, salaried employment, and central control of clinical activities may become the dominant form of practice. From this, he suggests that the chronically mentally ill, among others, may be excluded from this new system, "where cost consciousness may supplant compassion" (5, p. 149). The issue begins to transcend that of profession. Instead of an occupational organization, we can become an industrial organization in which we each deliver a specific service, have a specific job, and get uniform compensation. While the aim of healing has not changed, the position of the healer has changed or may change drastically. Our special status may not be as dominant or exclusive as it has been in the past. Our autonomy and self-regulating may be markedly diminished. However, our major work, illness—its treatment, cure, and prevention—continues.

"In all societies people diagnose sickness and adopt various methods of managing it . . . but all healers are not called doctors or physicians, nor are they usually considered to be professionals in any other sense than that of making a living from their work" (4, p. 3). It is difficult to define a profession. Occupations to which the word has been applied have nothing in common except the prestige and social or transferential power bestowed on the proclaimed professional. The designation of "professional" is related to that of "specialist," "licensee," or one who holds a certificate issued by the state. Thus society, the law, and the discipline itself may all define the term somewhat differently. Medicine is a profession as defined by law, society, and its own standards. Psychiatry is a branch of medicine. But the professional who professes to have certain knowledge, skill, and experience to perform specific duties is working in an occupation that is basically service oriented. In other words, medicine is work: work that society has esteemed and found prestigious, authoritative, and definitive. But medicine's preeminence is not a long-established one (about 100 years). Many healers throughout the world do not go to special schools to learn their work, trade, job, or discipline. Increased technology and the introduction of many specialized technicians who are not physicians present new challenges to existing professions. Some are viewed as threats to the existing status. Freidson sees a profession fundamentally as an organization and control of work.

Everett Hughes (6), another pioneering sociologist studying work and its relationship to society, emphasizes social role, occupational selection and its motivations, the identity tag of an occupation and its relationship to prestige, the education for a profession, the boundaries between professions, and so forth. The questions Hughes raises are deserving of further study today—in the new climate of the years that approach the twenty-first century. Should we concern ourselves with these issues? My answer is yes—we need such studies to help us gain perspective on the changing attitudes toward one of the medical professions, our specialty. Over 20 years ago Schatzman and Strauss (7) specifically studied and wrote about "A Sociology of Psychiatry: A Perspective and Some Organizing Foci." Their ideas are still significant and worthy of reconsideration.

Heskett, writing in the March/April 1987 issue of Harvard Business Review (8), discussed the service sector. He made no reference to profession or specialty as we know it, and yet his descriptions of the factors involved in service delivery systems in business sound familiar, e.g., target markets, positioning to meet customer needs, value and cost, competition, customer or customer acceptance, marketing, control and measurement of quality and cost, and productivity. Heskett noted:

Successful service providers have strategies in common that offer lessons to other companies. Among these are

Close coordination of the marketing-operations relationship.

A strategy built around elements of a strategic service vision.

An ability to redirect the strategic service inward to focus on vital employee groups.

A stress on the control of quality based on a set of shared values, peer group status, generous incentives, and, where possible, a close relationship with the customer.

A cool appraisal of the effects of scale on both efficiency and effectiveness.

The substitution of information for other assets.

The exploration of information to generate new business. (8, p. 125).

The language and concepts are similar to what we hear, see, and use frequently today. Are we a service delivery system, a profession, or a specialty? Are our patients customers?

Our profession, our Association, our leadership, and our members are all confronted by change at all times. We can despair, demand, become disillusioned or depressed, become reactive and regressive, or we can assess the situations and then, through creative planning and implementation, be assertive, forward looking, and upbeat. This has proven to be true in the past 7 years, when we have overcome obstacles and retained greater control of our professional lives. We can integrate knowledge from different fields, apply this knowledge to our profession, and influence other disciplines as they have been influencing us, provided we do not retreat to reactive, outworn, and despairing positions. By establishing open inquiry and by combining ideas from new terrains, we can turn the threats of change into new opportunities for success. The

issues we will face and that we are facing are many, e.g., expansion of care for the mentally ill; the problems of care, funding, and help for our ever increasing older population; the question of managed care facilities; the question of less care/best care; and catastrophic insurance coverage that may exclude care for psychiatric illness. Howard Goldman, at the exciting 1987 APA Federal Legislative Institute, noted that hoped-for changes require constant pressure and vigilance (personal communication). However, at times, this involves negotiation and trade-offs; compromise and redistribution are needed on such occasions, but these need not be the final words. Pressure for change can bring us closer to the attainment of our objectives.

Let me briefly discuss some additional curent issues that demand our attention and so are opportunities for creative action.

#### A MEDICAL STUDENT INITIATIVE

Young residents have concerns about their future and the future of our field. This situation is especially distressing when esteemed teachers and leaders emphasize all of the problems the field is encountering. The residents wonder: where are the ideals and goals that brought us to medicine? Where are the human concerns involved in working with the ill, the needy, the helpless, and the powerless? Are we losing the human touch when we become too mechanical, too regulated. and too involved in depersonalized mechanisms at the expense of the individual's uniqueness? Are we isolating ourselves from our patients when we do not have the time to listen to them, see them on an ongoing basis, and learn about their families, their lives, and their concerns? We cannot dismiss these questions with easy rejoinders. These concerns demand a hearing, the queries require thoughtful answers, and the models need buttressing lest the concrete dissolve into sand and water. Of course, we have dilemmassubspecialization, income, research support, hospital bed support, and relations with other medical specialties, other allied disciplines, governmental agencies, and consumer groups. But we can address these challenges and use them as opportunities for innovative planning and exploration of new possibilities. We have a responsibility to do this.

A recent study on "Medical Students' Beliefs About Nine Different Specialties" (9) gave us a view of how psychiatry was perceived by medical students in Great Britain. Some of their criticisms included the following:

[In comparison] with the eight other specialties, medical students believed that psychiatry had advanced least in recent years; psychiatrists were less stable than other doctors; psychiatry was the least expanding frontier of medicine; ... psychiatry had lowest status in medicine; psychiatry was most unscientific and imprecise; psychiatry was more of a waste of a medical education; psychiatrists

were fuzzy thinkers; psychiatry was unrewarding; psychiatrists were more concerned to establish rapport with their patients; and psychiatrists talked a lot but did little. Furthermore, the students thought that psychiatric treatment caused patients to worry too much; psychiatric facts were mere speculations; ... psychiatric treatment was basically fraudulent; few results were replicable; psychiatric theories were far removed from practice; research in psychiatry showed less patient improvement; psychiatrists tended to overconceptualise their patients' problems; psychiatry was more of an art than a science; psychiatric patients got better less often; there were too many doubts about psychiatry; ... psychiatrists were held in poor regard by other doctors; ... psychiatry was the least important area of medicine; and psychiatric patients tended to make more emotional demands than other patients. (9, pp. 1607-1609)

We may find similar attitudes in the United States. While some of these responses may indicate the stigmata about psychiatry that exist, we must pay attention to the implications of these attitudes. The picture of how we appear in the eyes of some British medical students challenges us to present our specialty in a more attractive and exciting fashion. We must begin a medical student initiative. These future physicians will be the main source of our referrals, our teammates, and our future residents. Seize the opportunities to lobby for psychiatry with them!

Nevertheless, I believe that our success in recruiting resident members in training is outstanding, perhaps even phenomenal. Also impressive is the trend in the last 7 years in the national resident matching plan. In 1980, 2.7% of medical students matched into psychiatry. This percentage has steadily increased so that in 1987, 4.3% of medical students (or 675 individuals) matched into psychiatry (S. Weissman, personal communication). If we consider additional students who enter psychiatric residency programs outside the match, we exceed even the just cited figures. However, we must pay close attention to another aspect of our medical student education initiative—most students, of course, do not enter our field but specialize in other areas, e.g., medicine, surgery, pediatrics, obstetrics, and family practice. In order for these future sources of referral to work effectively with us, they, in medical school, must respect and be familiar with psychiatry. We have to effectively communicate with them what we can do for them and their patients, the exciting developments of modern psychiatry, where our research is leading, and how we articulate with the basic and clinical sciences of medicine. Let me emphasize that we must have our best teachers involved with medical school teaching. They are the models. They can communicate the humanistic, interesting, involving aspects of psychiatry and yet be clear about the boundaries of psychiatry. They can act as advisors, mentors, consultants, and liaison representatives with other specialists. From this we can address other ways of implementing the medical student initiative, including curriculum planning and funding for such undertakings. Medical students deserve the best we have—they are our future and the future of medicine.

#### QUALITY EDUCATION AS A MISSION

Of course, we cannot diminish our research, clinical, and basic science emphases with our residents, younger colleagues, and more experienced colleagues. Quality education for all can be one mission we espouse.

President Truman, confronting a conflicting fiscal dilemma, was told that, on the one hand, a group of eminent economists advocated one position, but, on the other hand, another equally eminent group held to another position. His response was alleged to have been, "Give me a one-handed economist." I say, in appreciation of his dilemma, give us many hands. Let us see how these all can give us new views, new ideas, and new positions that will yield new opportunities. In the years to come we will have to define and emphasize who we are, what we are, and what we profess and do best. We can avoid scare tactics and platitudinous moralizing. We are physicians, clinicians, scientists, and teachers who stand for the basic rights of individuals to get quality treatment. We want to practice our profession in a way that allows us to earn a decent income and that protects us from capricious legal challenges which are time and energy consuming and which interfere with the competent, effective, empathic care of patients, with their families, and with our own

We have to face new realities; some of these have been effectively brought to our attention by Dr. Melvin Sabshin (10). We must communicate with our members, our residents and medical students, our colleagues in all branches of medicine, and our wise and experienced staff. We must recognize that even with many different groups in our specialty, we can learn from all and need not go "riding wildly in all directions" (11) if we work together, in unity, as our first woman President, Dr. Carol Nadelson, emphasized during her administration. Differences need not present polarities. With the right attitudes and orientations, with dialogue and mutual respect, we can have complementarities. There is enough for all of us to do and do well. While living in the realities of the present, we can appreciate the paths of the past and the plans for our future.

We are dealing with complexities and interrelationships of many variables that act simultaneously and in sequence. If we become too reductionistic and simplistic, we are courting danger. If we consider too many variables at the same time, we run the risk of getting lost in a maze of relevant issues. We need careful planning and setting of priorities, which are then implemented logically and rationally. What we decide on requires ongoing monitoring and follow-up so that we can consider alternatives if we need to. We also must be mindful of our limitations.

#### MULTIPLE OPPORTUNITIES

We are living in a new era. We are operating in a different climate and environment. Our challenges are many. So are our opportunities. We can attain our goals without compromising our standards of quality, decency, humanity, and caring.

There is a story currently told in Europe about the man who goes to the polyclinic and asks to see the ear-and-eye doctor. He is told this is not possible as there is either an ear-nose-throat doctor or an eye doctor. "No," he says, "I need an ear-and-eye doctor because I hear one thing and see something completely different" (12). When I first read this story it stimulated different thoughts in me. You may ask, What does this have to do with APA? Does it relate to our debates about subspecialization? Does it relate to the many messages we have heard about cost control, diagnosis-related groups (DRGs), for-profit and notfor-profit health care institutions, and malpractice reforms? To these, I answer yes and no. What I am saying is that we in APA tell what can be seen, and what we see can be told. We communicate with you and for you and want you to communicate with us.

We need to remind ourselves to go back to basics—to appreciate man—the uniqueness, richness, aesthetics, creativity. We need more than to understand biological mechanisms—we need the humane approach to man as a feeling, creating creature in a family, community, and social context, with a rich and unique past; this includes an appreciation of the arts, literature, music, poetry, and culture. How do these contribute to our individual lives and our personal developments? When traumas and other activities interfere, how do these skew our development or actualize our potential for growth and enhancement?

Goldsmith, in his discussion of "The U.S. Health Care System in the Year 2000" (13), noted that "predicting the future in an age of rapid social change is risky business. However, one thing can be confidently said about the American health care system in the year 2000: most of its ingredients—the patients, the professionals, the strains of scientific inquiry and technological development, and much of the capital—are already present." Goldsmith discussed the following in greater detail.

- 1. Demographics—"As the baby boom generation becomes caught up in the coils of degenerative illness, American society will experience an unprecedented wave of health care cost pressure for both acute and chronic care." Are we preparing to meet these challenges in the 12 years ahead?
- 2. The changing role of the hospital—"The hospital of the future will be transformed into the critical care hub of a dispersed network of smaller clinical facilities, physician offices, and remote care sites that may stretch out as far as 200 miles (320 km) from the core facility, connected by air and ground critical care transport and integrated by clinical information and patient monitoring systems."

3. Health professionals—"The remaining portion of this century will see a continued waning of the post-World War II 'seller's market' for physician services. . . . Falling office visit volume, heightened competition, and leveling our declining physician incomes—have only begun to be felt."

"The turn of the century will probably find us with a substantially underemployed specialty physician cadre.... Physician-to-physician relationships have already become significantly strained in many communities by competitive pressures, as physicians become progressively more reluctant to seek specialty consultation for fear of loss of patients.... [This] could prove to be a significant threat to the quality of clinical care" (13).

More physicians will practice in rural areas as the metropolitan area physician markets get saturated. Goldsmith noted that the physician supply growth will "provide physicians with more time to spend with their patients if they so choose, broadening and deepening patient relationships and tilting medical care away from pure technology" (13). The implications here are of great importance for psychiatry and training in psychotherapy.

- 4. Health care financing—This is the largest unpredictable outcome, as it contains policy and political considerations. "Growing patient economic exposure to the cost of care has been a common theme of the 1980s, permeating both public and private insurance systems" (13). The impact of large clinical data bases to help frame health care payment decisions is increasingly felt—Medicare, DRGs, and insurance coverage for catastrophic illness are in the forefront of the deliberations of our Congress today.
- 5. Health maintenance organizations (HMOs)—
  "An influential school of contemporary thinking holds that integrated systems of financing and providing health care, such as prepaid health care plans or health maintenance organizations..., will become the dominant health care financing vehicle in the United States." However, it is becoming apparent to industry and employers that what HMOs do, they can do themselves while also keeping conventional health coverage. Employee assistance programs and patient cost sharing are newer developments. However, we may find that more adaptive planning can reverse trends that seem to be developing now, especially working with consumer groups and coalitions.

However, troubling economic issues still remain, e.g., problems of the uninsured, the elderly, the care of the chronically ill, and the services to the one-parent family confront us and affect psychiatry and psychiatrists. Again, opportunities to confront these challenges are within our grasp.

#### OPPORTUNITIES FOR THE FUTURE

I wish to briefly focus now on the impact of the transition in health care on young physicians. The

American Medical Association's Council on Long-Range Planning and Development published its latest report on this topic on December 26, 1986 (14). This brief document is worthy of our study, and I am certain that forthcoming conferences on long-range planning and the future of psychiatry will address issues contained in the AMA report. We have to ask, What is the future of psychiatry in the medical profession? The escalating costs of medical education, the growing debt burdens, recent problems with institutional funding, and competition for residents and residency positions and even for admission to some medical schools remain with us. Issues dealing with career choices after internship, the growing supply of physicians (although the AMA Council reports the slowest growing specialties for the 1980s and the 1990s are projected to be radiology, general surgery, and psychiatry), alternative modes of practice, competition among physicians and from large health centers, business decisions versus professional decisions, ethical concerns, liability costs, and physician-hospital relations all provide challenges and opportunities for planning and possible control of rate, pace, and direction of change.

"The status of the medical profession could decline, and the profession could become a trade. Incomes may fall. Physicians are likely to lose their exclusive authority over clinical decisions" (14). Related to this is the strong possibility that "there will be an increasing separation between those who make economic decisions and those who make clinical decisions in medicine" (14). Physicians, residents, and medical students are threatened. What can we as the major organization for psychiatrists and psychiatry do to meet these concerns and still be advocates for quality care for patients, for supporting quality clinical and basic research, and for ensuring excellence in our various educational endeavors? The process of identifying the concerns, issues, and challenges is a first step. Now we must discuss, monitor, and consider various options. It may be too early to know what is to be done, but we can move when action is indicated, we can take steps to retain our professional viability. We can be open and flexible yet retain our basic values, high standards, ideals, and human concerns.

We will maintain our standards of excellence in the care of the mentally ill. We will expand our advocacy role on behalf of patients and their families. We will extend our active participation in psychiatric education at all levels. We will support and encourage individual, community, and public sector psychiatry. We will fight stigma and prejudice wherever it is found. We will assume leadership roles in research, quality care, and ethics, and we will strengthen our liaisons within all branches of psychiatry, with other medical specialties, and with other disciplines that relate to our work.

In recent years we have been appropriately concerned with many issues: economics, government relations, public information, forensic psychiatry, and professional jurisdictional matters. It is time for us to expand our perspective, to develop new opportunities for our colleagues and students, and to involve both them and ourselves in creative activities beyond our traditional areas of concern. As individuals, members of families, physicians, psychiatrists, and responsible members of society, let us work at further enhancing what we are already doing so well. The strength of our Association is in its diversity and multiplicity of missions. The challenges are many, but the opportunities are also there. We must provide leadership for the future and so ensure our ongoing success.

#### REFERENCES

- 1. Menninger W: Living in a Troubled World. Kansas City, Mo, Hallmark Editions, 1967
- Cohen D: Is community care the real answer? Listener, April 2, 1987, p 10
- Bierstedt R: Introduction, in Profession of Medicine. By Freidson E. New York, Dodd, Mead & Co, 1973
- Freidson E: Profession of Medicine. New York, Dodd, Mead & Co, 1973
- Bittker TE: The industrialization of American psychiatry. Am J Psychiatry 1985; 142–154
- Hughes E: The Sociological Eye. New Brunswick, NJ, Transaction Books, 1984
- 7. Schatzman L, Strauss A: A sociology of psychiatry: a perspective and some organizing foci. Social Problems 1966; 14:3–16
- 8. Heskett JL: Lessons in the service sector. Harvard Business Review, March-April 1987, p 125
- Furnham AF: Medical students' beliefs about nine different specialties. Br Med J 1986; 293:1607–1610
- Sabshin M: The future of psychiatry: coping with "new realities," in Our Patients' Future in a Changing World. Edited by Talbott JA. Washington, DC, American Psychiatric Press, 1986
- Grinker RR Sr: Psychiatry rides madly in all directions. Arch Gen Psychiatry 1964; 10:228–237
- Easterman M: The dangers of prejudging Mr Gorbachev's new reality. Listener, March 26, 1987, p 4
- Goldsmith JC: The US health care system in the year 2000. JAMA 1986; 256:3371-3375
- Council on Long-Range Planning and Development: Health care in transition. JAMA 1986; 256:3384–3390

#### Robert O. Pasnau, M.D., One Hundred Fifteenth President, 1986–1987

Norman Q. Brill, M.D.

When Robert O. Pasnau was born in Mason City, Iowa, on July 8, 1934, his father, who was the supervisor of the American Telephone and Telegraph operation there, and his mother, who was the daughter of a Presbyterian minister in Burlington, Iowa, could never have predicted that their firstborn would become one of America's leading psychiatrists. They probably expected him to enter what, for a Midwesterner, would be a more traditional occupation or profession. His parents were native Iowans who had met when they were both members of a little theater group.

His mother was the high school Latin teacher and the church organist. She taught little Robert to play the piano and was responsible for his developing a love of music, which has persisted all of his life. His father had had a strong religious upbringing, was active in the Boy Scout movement, and enjoyed outdoor activities, exposing Robert to the joys of fishing, swimming, and camping. It was a closely knit family. Robert and his younger brother were to enjoy a happy childhood with loving, attentive parents.

When Bob was 3 years old, and shortly before the birth of his brother, John, the family moved to Princeton, Ill., because of his father's job transfer. They moved with mixed feelings because they had been looking forward to moving into the house in Mason City that his father had just finished building. One year later, when his father was promoted to personnel director for American Telephone and Telegraph in Chicago, they moved to suburban Park Ridge, and it was there that Bob grew up.

Bob was a good boy. He had a happy disposition, was a good student, and was a joy to his parents. Tragedy struck when Bob was 9 years old. His mother, whom he loved dearly, developed cancer of the colon, was in and out of the hospital, and died at Christmas in 1945, leaving his father, who never remarried, to care for the young boys.

Bob kept grieving and suffering inside and for years dreamt of his mother's coming back. Witnessing her

suffering was one factor that led to his interest in becoming a doctor. His tendency to keep his feelings inside may have been related to his developing headaches in adolescence. Anger and disappointment were never expressed—and may even have contributed to his developing mild hypertension later in life.

The early promise many children show is often never fulfilled, but Bob, who graduated from the Maine Township High School as valedictorian, did fulfill the prediction of his classmates, who voted him as the one "most likely to succeed." He turned down scholarships to Harvard College and Wesleyan University to go to the University of Illinois, on a full scholarship, in order to be close to high school friends who were going there. He did well in college, enjoyed life, loved science courses, was elected president of his fraternity (Phi Kappa Sigma), and helped support himself by playing piano with a dance band that he organized. As a premed student he majored in chemistry, but he was also interested in philosophy. He made A's and was elected to Phi Beta Kappa in his junior year.

He was accepted at the University of Illinois Medical School after just 3 years of college and was granted a B.S. degree after completing his second year of medical school in 1957. He had planned to become a pediatrician but changed to psychiatry in his junior year after having been exposed to an outstanding group of psychiatrists in the course of his studies. Dr. Harold Visotsky was the first psychiatrist who ever interviewed him; it was for a summer job in a project investigating the neurological and psychiatric effects of scopolamine and atropine. Dr. George Pollock was his teacher in the first-year course in psychiatry. Later on, Dr. Hugh Carmichael recognized Bob's special talent in working with psychiatric patients and encouraged him to go into that specialty. He is still sentimental about having been exposed to Drs. Jack Weinberg, Francis Gerty, Mel Sabshin, and Roy Grinker. Identification with these great men and his own innate talent in both neurology and psychiatry were determining factors in his subsequent impressive career. Unlike so many who struggle through their 4 years in medical school, Bob enjoyed it. Learning was easy for him, and he finished in the upper fifth of his class.

His internship at the University of California, San Francisco, Medical Center, during which he was paid \$196.00 a month, and his subsequent residency in

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psychiatry at UCLA were related to things other than climate and reputation. California was where his future wife Jan and her family lived and the place he would live after graduation from medical school.

After his sophomore year in college in 1954, Bob obtained a summer job in Los Angeles selling books from door to door. It was in a Spanish class he was taking at UCLA that he first saw Janet Worden, who was to become his wife. Jan had been born and raised in San Francisco; both of her parents were native Californians. She was a student at the Berkeley campus of the University of California but was living in Hermosa Beach with her mother that summer while attending UCLA.

It was love at first sight, and Bob courted her that summer by taking her to Hollywood Bowl concerts—in the  $50\phi$  seats. (To this day, they continue to attend regularly—now in box seats.) They were engaged during Christmas that year and were married in August 1955, just before he started medical school. By the end of his first year in medical school their first child, John, was born. William, their second child, was born shortly after Bob started his internship, and James, their third child, was born in 1963 during Bob's residency at UCLA. Some years later, Robby was born—the fourth son in a row.

As a resident, Bob endeared himself to all who knew him. He was outgoing and warm and had the ability to make friends easily. These characteristics, in addition to his sensitive, outstanding work with patients, prompted me to appoint him chief resident during his fourth year at the UCLA Neuropsychiatric Institute and to give him an appointment as a junior faculty member. He very generously credits me with having been a strong influence in directing the course of his career.

On July 1, 1964, Bob joined the U.S. Navy as a lieutenant commander and was assigned to the San Diego Naval Hospital. He served for 2 years, in the second year as chief of outpatient psychiatry. It was while he was in the Navy that the second great tragedy of his life occurred—the death of 2-year-old James by accidental poisoning. Bob and Jan have never completely recovered from this terrible experience of losing a child. It was not just the loss and grieving, but the feeling of guilt that such a thing had been allowed to happen. Bob related how, much later, he dreamt that his mother and son were alive. Bob and Jan received support from each other and counseling from friends and colleagues. One close friend, a child psychiatrist, flew across the country to talk to the older children about the tragedy and to help them express their feelings. Bob completed his 2 years in the Navy and returned to UCLA in July 1966 as an assistant professor and immediately assumed responsibility for coordinating the residency program.

From that point on, Bob's career in psychiatry was one of steady academic advancement and organizational involvement that eventually led to his becoming President of APA. By 1978 he had advanced to the

rank of full Professor in the Department of Psychiatry at UCLA Neuropsychiatric Institute.

With a unique ability to be involved in many different activities at the same time, in addition to the teaching and other academic and administrative demands, Bob managed to be a founding member of the American Association of Directors of Psychiatric Residency Training and the American Association of General Hospital Psychiatrists. Five years after being elected to fellowship in the American College of Psychiatrists, he was serving as its President; he also served for years before and afterward on its Board of Regents. He was also active in the American Psychosomatic Society, the Association of Academic Psychiatrists, the Pacific Rim College of Psychiatrists (which he helped form), and the Southern California Psychiatric Society, which honored him by electing him President in 1975.

He has been the recipient of many honors. As a resident, he was awarded the Gold Medal for Scientific Writing by the Academy of Psychosomatic Medicine in 1963 for his report on "Therapy of Ulcerative Colitis in Children" (1). Other honors came from the Los Angeles Community Cancer Control Organization, the APA Assembly (where he was the Speaker in 1980), and the American College of Psychiatrists after his term as President.

Although Bob had joined APA as a resident in 1962, it was not until 1973 that his active involvement in the organization began. He was Director of Residency Education at UCLA at the time and was appointed to the APA membership committee and to the faculty of the 25th Institute on Hospital & Community Psychiatry. From there on, his involvement became more intense and included serving in the Assembly of District Branches and on committees concerned with reorganization, personnel policies, long-range planning, insurance for mental illness, the APA Biographical Directory and Manpower Survey, budget, nomenclature, and the Key conferences. He often served as committee chair. Eventually, he served as Chair of the Councils on National Affairs and Internal Organization and the Joint Reference Committee and as a member of the Board of Trustees (and its Executive Committee) before his election as Vice-President in 1982 and President-Elect in 1985. At the annual meeting in 1986 he became President.

The adjectives most used in describing Bob by those who know him are "warm," "friendly," "sincere," "interested," "generous," and "kind." He is admired for his ability to make friends with people of all cultures. He is cordial, no matter how pressed. He can be expected to give a sympathetic and reasonable consideration of any issue. His personality has served him well on the innumerable committees he has chaired. He is polite, unbiased, and willing to listen to any position. He is sensitive to others' feelings and so diplomatic that some of his close friends have complained that sometimes they can't decide which side of a controversy he is on. His reputation is enviable.

There is no one I know who speaks badly of him. He is remarkable at avoiding alienation or factionalism.

As APA President, Bob contributed to resolving conflicts between the Assembly and Board of Trustees and had to deal with objections that were raised about adding the diagnoses of premenstrual dysphoric disorder and masochistic personality disorder to the revision of DSM-III. There was fear that all abused women would be given a diagnosis of a personality disorder and that women with premenstrual tension would be considered mentally ill. Controversy surrounding the publication of a treatment book by APA was met by the decision to issue it as a task force report. While the need for a guide to treatments for specific disorders was admitted, Bob was sympathetic to the fear that psychiatrists had been "cookbooked," while realizing that if they did not write standards, bureaucrats or health care organizations would.

He saw how psychiatrists who are held responsible in the final analysis for the quality of care were confronted with the problem of interference from government and business in their attempts to deal with rapidly escalating costs. APA was also obliged to deal with the increasingly high cost of professional liability insurance, which resulted in part from the grossly excessive judgments that the courts were awarding.

Major successes achieved by APA during Bob's term of office were the work with Congress in trying to reverse the discrimination against medical payment coverage for psychiatric disorders and the integrations of effort with the AMA to ensure that comprehensive mental health benefits were at parity with those for physical illness. One indication of improved collaboration with the AMA is the inclusion now of two APA members on AMA councils.

Bob advocated closer ties with the AMA and hoped they would lead AMA to lend its weight to dealing with the issues and problems confronting psychiatrists and induce more psychiatrists than the current 30% to join the AMA (as he did). He was troubled by the misrepresentation of psychiatry in the media and urged action to eliminate it. As his presidential theme, he chose "Psychiatry in Medicine," reflecting his dedication to the full acceptance and integration of psychiatry as a medical specialty.

Bob has had occasion to witness psychiatry being criticized or ignored by medical colleagues and has devoted his energies to a better recognition of the role of emotional factors in illness. The major portion of his professional activities has been in teaching and research in this area. He developed the Consultation-Liaison Service at UCLA and achieved closer integration of psychiatry and medicine.

He has earned the respect of medical colleagues on other services and is often called upon for assistance in their dealings with patients who have emotional disorders that are superimposed on physical illnesses. He is deeply concerned with the provision of good patient care and is truly eclectic in his approach.

He has not only written extensively on various aspects of the mind-body interaction but has been invited by agencies and institutions in many countries to give lectures and consultations. He serves on the editorial boards of many professional publications. His scientific articles number over 100, he is the author of nine books and monographs and numerous audiovisual tapes, and he is a reviewer for a number of psychiatric journals.

In his present position as Director of Adult Psychiatry at UCLA Neuropsychiatric Institute, Bob is responsible for three adult units, a large outpatient program, the Consultation-Liaison Service, the Admitting and Evaluation Service, and the Adult Day Treatment Service. His main interest, psychosomatic medicine, goes back many years to his report "The Therapy of Ulcerative Colitis" in children.

He is optimistic about the future of psychiatry and believes that the many recent technological developments in brain imaging and psychopharmacology will contribute to the much needed remedicalization of psychiatry.

Like his father, he worked with his lovely, loving wife to provide a happy, supportive home for their three sons. He is also like his father in his long-term interest in the Boy Scouts and his service as Scoutmaster of Los Angeles Troop 36 for 7 years when his boys were young. The two older boys are married, and the youngest attends Tulane University.

It has been my pleasure to have been associated with Bob from the time he first applied for his residency at UCLA. He and Jan have been a joy to know and are well deserving of all the good things that are said about them.

#### REFERENCE

Pasnau RO: Therapy of ulcerative colitis in children. Psychosomatics 1964; 5:137–143

#### A Neuropsychological Hypothesis Explaining Posttraumatic Stress Disorders

Lawrence C. Kolb, M.D.

The author reports findings from recent psychophysiological and biochemical research on Vietnam combat veterans with chronic posttraumatic stress disorder. Applying these data and the analogy of the known functional and structural defects in the peripheral (cranial) sensory system consequent to high-intensity stimulation, he hypothesizes that cortical neuronal and synaptic changes occur in posttraumatic stress disorder as the consequence of excessive and prolonged sensitizing stimulation leading to depression of habituating learning. He postulates that the "constant" symptoms of the disorder are due to the changes in the agonistic neuronal system which impair cortical control of hindbrain structures concerned with aggressive expression and the sleep-dream cycle.

(Am J Psychiatry 1987; 144:989-995)

Ontroversy continues to rage over the posttraumatic stress disorders. Are the symptoms evidence only of a consistent process set in motion following any major threat to one's security? Does the condition merit consideration as a clinical entity to be classified separately in our diagnostic scheme? Are the stress disorders merely variants of other personality disorders? Is massive psychological trauma the etiologic agent? May the condition be induced in adulthood without preceding genetic and/or constitutional deter-

the phenomena of the stress disorders only reflections of psychological processing of information signifying existential threat, or are they representative of other (possibly preceding) psychopathological and/or neural changes?

minants or early traumatic experiences? In short, are

#### RECENT CLINICAL OBSERVATIONS

It is my work over the past 9 years with men who have come to suffer the severe forms of chronic posttraumatic stress disorder that I shall report in this paper. Due to my World War II clinical experiences in diagnosis and treatment of patients with acute combatinduced posttraumatic stress disorders, it was possible for me to quickly recognize the chronic and delayed forms of these disorders in many hospitalized men. The data to be reported here come from personal examination and engagement in treatment of more than 300 Vietnam veterans with chronic or delayed posttraumatic stress disorder, 10 prisoners of war of World War II, and a sizable number of patients whose chronic and delayed posttraumatic stress disorder from the Korean and World War II conflicts had been missed—as well as many noncombatant Vietnam-era veterans without posttraumatic stress disorder in hospital in- and outpatient services. The majority of these patients had experienced long and high-level combat exposure. My impression is that the more disabled patients, with predominantly dissociative, "catetenoid," or psychosomatic symptoms, have come or have been brought to the hospital services for years.

Among the earlier and more severely disturbed patients were a number of men with socially impairing dissociative states (flashbacks) or panic attacks. Many indicated the persistence of a startle reaction with associated physiological arousal on exposure to sharp sounds produced by helicopters or other explosive

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noises. When pushed to describe their combat experience, these men often provided sketchy accounts without associated affect.

For 18 of these patients, treatment using a modified form of narcosynthesis directed at verifying the existence of repressed emotion was initiated to provide emotional "de-repression." An audiovisual recording of these patients' behavior during the treatment was made to be used as confrontation in later psychotherapy. The narcosynthetic technique was also modified to test the existence of a conditioned emotional response. Rather than verbal suggestion, which was used in treatment of severely, acutely disturbed patients during World War II, each patient was exposed to a brief train of combat sounds as the initiating stimulus for abreaction.

Fourteen of the 18 men exposed to a moderateintensity combat sound stimulus of 30 seconds while in arousable pentobarbital anesthesia immediately responded with time regression and reenacted a Vietnam combat experience with intense emotional abreaction of the affects of fear, rage, indignation, sadness, and guilt. No responses were elicited by musical stimuli or by silence, and two noncombat veterans exposed to the sound train also failed to abreact. The characteristics of this group of men and their responses have been described in some detail elsewhere (1). The emotionality was so evident during abreaction that an effort was made to monitor various physiological systems. No clear-cut abnormalities were discovered in the subnarcotic state, presumably because the injected drug obscured related organ responses during the emotional storm.

#### RECENT PSYCHOPHYSIOLOGICAL RESEARCH

To examine the hypothesis that autonomic arousal did indeed occur following the startle reactions on exposure to a meaningful sound stimulus reminiscent of combat, I initiated a collaborative study with Prof. Edward Blanchard of the Stress Laboratory of the State University of New York at Albany. Initially, he and his colleagues, Thomas Pallmeyer and Robert Gerardi, exposed 12 combat veterans who met the operational criteria of DSM-III for posttraumatic stress disorder to a train of combat sounds of varying intensity given at varying times and interspersed with periods of music and silence (2). The veterans were in a fully conscious state, and their diastolic and systolic blood pressure, heart rate, finger-tip skin temperature, and galvanic skin reflex were monitored. In addition to the combat sounds, the subjects were also exposed to an arousal sound. They were also given an intellectual stress test and a variety of standardized psychological tests. Their responses to these instruments were compared with those of control subjects tested in precisely the same manner. The control groups consisted of 10 Vietnam combat veterans without posttraumatic stress disorder, 16 Vietnam-era noncombat veterans (12

with and four without psychiatric disorders), 11 sameaged university students, and 14 civilians with other anxiety disorders. Since that study, Blanchard et al. (3) have examined a total of 91 combat veterans—57 with and 34 without posttraumatic stress disorder.

All participants took the following psychological tests: State-Trait Anxiety Inventory, Beck Depression Inventory, and Buss-Durkee Hostility Scale (2). The veterans scored significantly (p<.001) higher than control subjects on all measures, indicating more pa-

thology.

The physiological data analyzed to date have yielded the most interesting findings. Analyses of the six physiological responses revealed three statistically significant (p<.001) differences between the veterans with posttraumatic stress disorder and the control subjects: heart rate, systolic blood pressure, and diastolic blood pressure. In each instance the veterans with posttraumatic stress disorder showed more arousal in response to the combat sounds than did the control subjects. The arousal of many men was so distressing personally that they terminated the experiment at low levels of sound intensity. The later study (3), using a single cutoff rate for highest heart rate response following exposure to combat sounds, found that heart rate response alone accurately identified 40 (70.2%) of the 57 combat veterans with posttraumatic stress disorder and 30 (88.2%) of the 34 combat veterans without posttraumatic stress disorder. Using this cutoff resulted in only six false-positives among the 34 veterans without the disorder. Four of these false-positives would have met the diagnostic criteria for posttraumatic stress disorder in the past and were therefore considered clinically remitted. Further analysis using the other physiological measures is now underway in this group of veterans.

There are two other reports of psychophysiological assessment of combat veterans with chronic posttraumatic stress disorder. Dobbs and Wilson (4) compared the psychophysiological responsivity to audiovisual stimuli of two groups of World War II veterans with the chronic posttraumatic stress disorder of combat (13 men considered socially compensated and eight men considered socially decompensated some 10 years after their war experiences) with that of a group of 10 noncombatant university students. Increases in pulse and respiratory rate as well as a decrease in alpha rhythm occurred in the vast majority of the combat veterans when exposed to the audiovisual stimuli but not in the control group. Many of the men in the socially decompensated group were unable to complete the test, leaving the experimental setting before the sound stimulation was completed.

Malloy et al. (5) compared the physiological responses of 10 Vietnam combat veterans with posttraumatic stress disorder, 10 noncombat veteran control subjects, and 10 psychiatric inpatients without posttraumatic stress disorder. As stimuli they presented both combat-related and noncombat audiovisual scenes.

Physiologically, during exposure to the combat stress scenes the veterans with posttraumatic stress disorder showed an increase in heart rate and skin resistance; these increases did not occur in either group of control subjects. Multivariate analyses of the various physiological, behavioral, and self-report observations successfully discriminated all of the Vietnam combat veterans with posttraumatic stress disorder from all of the control subjects.

To summarize, three entirely independent and unrelated studies of American combat veterans from two wars with the clinical symptoms of posttraumatic stress disorder exhibited more abnormal behavioral and physiological arousal than control subjects from a variety of groups when exposed to meaningful stimuli reminiscent of combat (6). Thus, psychophysiological assessment offers strong potential not only for diagnostic identification of a special subgroup of patients with war-induced posttraumatic stress disorder but also for assessment of the severity of the disorder. The total number of subjects with posttraumatic stress disorder now tested from the three studies equals 88, and the number of control subjects is now 64.

#### SIGNIFICANCE OF FINDINGS

These findings define a subgroup of combat veterans with chronic, delayed, or remitted forms of posttraumatic stress disorder who have a persisting conditioned emotional response to stimuli reminiscent of battle. We may postulate that in such men there exists not only an ongoing perceptual abnormality (impairment of the ability to discriminate specific sensory inputs associated with the traumatic event) but also excessive autonomic arousal of central adrenergic origin.

Two other research studies suggested abnormal physiological functioning in posttraumatic stress disorder. Wenger (7) carried out extensive psychophysiological testing to examine the assumption that differences in autonomic balance existed between 298 World War II combat flyers convalescing from what was then designated in the Air Force as "operational fatigue" and 482 aviation students in training who had not yet been to combat. He recorded without stimulation 20 different tests of autonomic function and found that nine attained differential statistical significance and supported his hypothesis that excessive sympathetic function is characteristic of operational fatigue.

Mason et al. (8) reported on separating out neurochemically a group of nine men with posttraumatic stress disorder and depression from 10 others with major depressive disorders. The former had unusually high urine levels of norepinephrine as well as a discriminating norepinephrine-cortisol ratio.

Pertinent here are some clinical observations reported in a paper cited earlier (6). Of seven men whom I had instructed to use a tape of combat sounds for desensitization (initially to be played at subliminal

intensities), none was able to do so without arousing somatic responses. One, angered at his failures, played the tape at high intensity on his sound system, dissociated cognitively, and in a violent rage tore apart his workroom. Beyond that, the long-term follow-up of patients in continuing treatment has demonstrated time and again the recrudescence of the constant symptoms of the condition, as defined by Kardiner and Spiegel (9). These symptoms arise in the face of either a current stressful life event involving threat or loss arousing once again emotions of terror, sadness, or anger—or a threat to the individual's own body by acute illness or an accident. On exposure to such stimuli, patients with posttraumatic stress disorder respond with immediate and excessive physiological arousal, particularly in their cardiovascular and neuromuscular systems, and are at risk for cognitive dissociation.

We have, then, a clinical condition induced by either a single massive psychological assault or by recurrent or continued exposure to experiences associated with violent death, destruction, and/or mutilation of others, which induce high-intensity emotional arousal. The emotions of fear, terror, and helpless despair are followed by a number of constant yet repetitive behavioral, cognitive, and physiological processes. In many, withdrawal from exposure, nonrecurrence of exposure, or avoidance of memory-arousing experiences similar to the initial stressing events is followed by extinction of these phenomena. In some the extinction is only partial; somatic arousal still may be observed when the gross clinical symptoms have remitted. Other patients go on to suffer delayed, recurrent, or persistent display of the consequences of the overwhelming emotional assault. I emphasize "emotional" and not "psychological." Emotion implies stimulus sacilitation. Depending on the intensity of stimulation, it may facilitate or destroy cognitive processing. Among those who fail to recover from the initial assault are a group who suffer recurrent or persistent clinical symptoms and demonstrate evidence of a conditioned emotional response.

#### CONDITIONED FEAR IN ANIMALS

Much has been learned about conditioned fear in animals that seems directly relevant here. Directly pertinent to chronic posttraumatic stress disorder are the studies of Anderson and Parmenter (10) of the long-term effects of experimentally induced neurosis in animals. These researchers followed both sheep and dogs over 12 years after induction of experimental neuroses in which electric shock was used as the unconditional stimulus and the sound of a metronome was used as the conditioning stimulus. The long-term behavioral and physiological hyperactivity of these animals was remarkably similar to that noted in the chronic posttraumatic stress disorder of combat veterans with conditioned emotional response. This hyperactivity included hyperalertness to touch, the startle

reaction to sound (crouching, trembling, running, and even defecation), a "set" toward overreaction, generalization of the reaction to other stimuli, and restlessness. Some animals later developed a state of immobility when placed in the experimental room, as though they were afraid to move. Also noted in these animals over a period of years was continued cardiac and respiratory dysfunctions. Tachycardia occurred when the animals were brought to the laboratory.

In their work on traumatic avoidance learning in animals, Solomon and Wynne (11) stated, "In the case of intense anxiety established with the support of an initial pain-fear reaction, we believe that the classically conditioned responses have become incapable of complete extinction." Further, they postulated a relatively permanent "decreased threshold phenomenon or sensitization phenomenon," which leads to "an increase

in probability of occurrence."

That environmental experiences provide the sensory stimulation on which both functional and anatomical development of the brain depends is now clearly evident from neurobiological research. These findings became possible only through the advances in electrophysiological, neurochemical, and imaging techniques. For instance, Hubel and Wiesel (12) demonstrated that the visual cortex (area 17) of both cats and macaque monkeys fails to develop physiologically if they are deprived of monocular vision at critical periods of early life. Neurons from the opposite geniculate nucleus tend to grow into visually deprived and undeveloped columns of cortical dominance. These findings suggested to the researchers that a form of competitive interaction takes place between the neuronal growth of the two opposing visual pathways. Stimuli from the eye not deprived of vision induce electrophysiological activity in the maldeveloped area. These maldevelopments were confirmed neuroanatomically by autoradiographic techniques.

Studies of learning processes in the simple nervous system of the snail Aplysia californica by Kandel (13) have made it clear that synaptic function changes depending on the nature of the learning process. Thus, during habituation of the gill reflex of Aplysia, when the animal learns "to recognize and ignore a particular stimulus because its consequences are trivial" (a primitive form of perception), many synaptic connections become inactive without the intervention of reverberating circuits as in a closed set of neurons. Kandel's studies on sensitization learning are particularly relevant to questions related to posttraumatic stress disorder. Sensitization enhances the animal's attention to threatening stimuli. It involves postsynaptic facilitation mediated by axo-axonic synapses. If habituation has been achieved, sensitization reverses the presynaptic and behavioral depression produced by either short- or long-term learning. Although change is evident electrophysiologically, it is not now fully understood what occurs at the synaptic terminals during the learning process. Kandel suggested that neurochemical changes must occur at synaptic connections without gross neuroanatomical rearrangement. Kandel's sensitization experiments have not been carried to the point of excessive stimulation over long periods of time.

Reiser (14) recognized the relationship between the new neurobiological understandings and psychological processing and illustrated this in an analysis of a typical case of social stress. My clinical and research data derive from the consequence of overwhelming, often repeated catastrophic stress. Such stress requires that we go beyond the ordinary learning experiences or their absence and examine the consequences of excessive sensitizing stimulation on the neural structure.

#### NEURONAL EFFECTS OF HIGH-INTENSITY STIMULATION

That excessive external stimulation might affect neuronal structure has been postulated in the past. Freud (15) described a "stimulus barrier" consisting of a series of neuroanatomical structures—including the skin, the peripheral sense organs, and an internalized neuronal layer—developed to protect organisms from excessive and destructive external stimulation. Miller (16) brought together the physiological and psychological data pertaining to excessive stimulation under the rubric of overload of information processing. In general, the data indicate that as information input increases, information output initially increases but gradually falls behind at the level of channel capacity. With further increases in input, output decreases to complete nonfunction and psychological confusional states occur. Before that, a variety of efforts at adaptation to overload take place; these are evident in obvious errors, omissions, etc. Possible central neuronal structural (neuroanatomical) change as the result of such overload has not been studied.

Nevertheless, both clinical and laboratory data exist that demonstrate both functional and structural change following high-intensity stimulation of the peripheral nervous system. The known consequences of such stimulation for the acoustic system provide an excellent model to conceptualize central neuronal change. Clinical observations (17, 18) have established that such stimulation—either remittent or of long duration—causes deafness of varying types and duration. Clinically, such loss of function may occur acutely, may be temporary, or may be permanent; these outcomes relate to both the intensity and the duration of the sound stimulation. Thus, volunteers exposed to 110 to 130 decibels for periods of 1 to 64 minutes consistently develop temporary high-tone hearing loss. In animal experimental studies of induced noise deafness after excessive sound stimulation, light microscopy has demonstrated initial changes in the external hair cells in the form of deformation of swelling of the cell body. With more severe injuries, other cells (pillar, Deiters' and Hensen's), including the internal hair cells, are damaged, and eventual cochlear. neuronal atrophy ensues. A variety of neuronal biochemical changes have also been identified as following the stimulus trauma. From these studies it has been suggested that moderate intensities of acoustic stimulation lead to increased metabolic activity. If excessive, the changes proceed to exhaustion of enzymes and glycogen stores, diminished oxygen tension, decreased energy output, irreversible anatomical change, and permanent deafness.

The emerging evidence of the existence of psychophysiological, neuroendocrine, and neurochemical abnormalities in chronic posttraumatic stress disorder outruns the potential of the current psychological explanations derived from psychoanalytic or learning theories. Confronted with the phenomenology of acute cases of war neuroses, Freud (19) stated, "The war neuroses insofar as they are distinguished from the ordinary neuroses of peacetime by special characteristics are to be regarded as traumatic neuroses whose occurrence has been made possible by a conflict in the ego." The conflict was perceived as occurring between the individual's striving to maintain his moral integrity as a soldier against the drive for self-preservation. The breakdown was perceived as due to the overwhelming of the psychological defensive structure of the exposed. Plagued by the challenge to both dream and libido theory in the face of the repetitive dreams and nightmares of combat, psychoanalysts later offered the drive for mastery through repetition as an explanation for these symptoms as well as for related neurotic and characterological changes (20).

From their examination of many patients with chronic war neurosis from World War I, Kardiner and Spiegel (9) came to the conclusion that the condition was a "physioneurosis." They suggested that the startle reaction seen in the patients with chronic neurosis was due to "conditioning" and that the existence of this pattern was central to understanding patients with chronic disorders as the cause of the irritability and the psychosomatic symptoms. To them, the chronic war neurosis was different from social neurosis in that the central focus of distress in the former rested in the individual's difficulty with his body image—his somatic functioning—and not with social conflict. The personality reactions were considered secondary and reactive to the physioneurosis. This hypothesis more satisfactorily covers most of the criteria needed to explain the observed symptoms than do others.

Dobbs and Wilson (4) concluded that there existed "remarkable similarity of the behavioral and physiological responses of the war neuroses to those produced experimentally in animals through conditioning." They suggested that sounds and sights simulating those of combat serve as conditioned stimuli to induce the self-preservative emotional responses of fight, flight, or paralysis, which become the conditioned responses. They did not attempt to explain the coexisting personality reactions of their patients.

Elaborating on this hypothesis, Keane et al. (21) offered a two-factor learning theory of psychopathol-

ogy to explain posttraumatic stress disorder psychopathology. Their two-factor theory relies both on symptom explanation through classical conditioning (through association a fear response is learned) as well as on instrumental learning principles (individuals learn to avoid cues that arouse emotion). This hypothesis accounts for the startle reaction in posttraumatic stress disorder as well as its arousal by a variety of stimuli that the individual has associated with the traumatic event-sounds, smells, and a wide variety of visual perceptions, including people. Keane et al. recognized that posttraumatic stress disorder victims display a much wider range of symptoms in that they respond to other crises not associated with the event. To explain this phenomenon, they invoked higherorder conditioning and generalization for those symptoms not definable by their two-factor theory. I have discussed and critiqued these various explanations in a paper presented during a National Institute of Mental Health workshop on delayed effects of posttraumatic stress disorders held in April 1986.

#### A NEUROPSYCHOLOGICAL HYPOTHESIS

Using the analogy of the effect of excessive stimulation on the contact barrier leading to change in neuronal function and/or structure, we can easily accommodate the symptoms and signs of posttraumatic stress disorder within traditional neuropsychological theory (22). The primary result of excessive emotional stimulation is its effect on the function and perhaps the structure of the cortical neuronal barrier, particularly as it concerns control of aggressivity. Such stimulus overload occurs when the human organism's capacity to process information signaling threat to life overwhelms the cortical defensive structural processes concerned with perceptual discrimination and effective adaptive responses for survival. Such stimulation may be thought to first lead to synaptic changes related to the process of neurophysiological sensitization, as described by Kandel (13). If continued at high intensity and repeated frequently over time, the processes may lead to depression of those synaptic processes which permit habituation and thus discriminative perception and learning. As Kandel has suggested, subtle neurochemical changes may occur in synaptic functions that currently defy detection by available methods. We cannot exclude the potential of actual neuronal death. Sapolsky et al. (23) reported hippocampal neuronal death in cells with high glucocorticoid receptors—interpreted as the result of response to stress over time.

The neuronal synaptic structures affected are probably located in the temporal-amygdaloid complex concerned with agonistic behavior; these structures are stressed by recurrent intensive stimulation. They may recover, be temporarily impaired, or undergo permanent change, which is known to occur in the peripheral (acoustic) sensory system.

In terms of clinical expression in behavior, the individual reverts (regresses) to a state of hypersensitivity in which a multitude of stimuli, both internal and external, lead to arousal. Recurrent intensive emotional arousal both sensitizes further and simultaneously disrupts those processes related to learning and habituation. This leads to reappearance or intensification of existing symptoms.

With excessive cortical sensitization and diminished capacity for habituation of the agonistic neuronal system, lower brainstem structures, such as the medial hypothalamic nuclei and the locus ceruleus, activated by the neurotransmitter norepinephrine (24), escape from inhibitory cortical control. Through their extensive cortical and subcortical connections, they, in turn, repeatedly reactivate the perceptual, cognitive, affective, and somatic clinical expressions related to the original traumata. Thus, in the face of perceived threats there occurs excessive sympathetic arousal including neuroendocrine disturbances as well as behavioral expressions of rage and irritability and repetitive cortical reactivation of memories related to the traumatic events. The latter are projected in the daytime as intrusive thoughts and at nighttime in the recurrent traumatic nightmares of posttraumatic stress disorder in all forms. The "constant symptoms" of posttraumatic stress disorder, then, are explainable as expressive of cortical synaptic change related to those processes which underlie sensitization, learning, and habituation.

It may well be that other central neuronal changes occur that underlie certain other features of chronic posttraumatic stress disorder. Hoppe and Bogen (25) have likened the alexithymia of commissurotomized patients to that of survivors of the Nazi concentration camps (chronic posttraumatic stress disorder) and psychosomatic patients.

The hypothesis presented here of functional change in neuronal and synaptic cortical processing of intense memories of aversive stimulation allows an understanding of the variegated symptom expressions of the condition. We may define the symptoms of posttraumatic stress disorder as 1) impaired perceptual, cognitive, and affective functions, 2) release of functions, 3) reactive affective states and avoidance behaviors, and 4) restitutive symptoms and behaviors.

The *primary symptoms*, due to cortical neuronal change, are those of impairment of perceptual discrimination, lessened capacity to control agonistic impulses, and, perhaps, affective blunting. Discrimination of threatening stimuli is less accurate, as demonstrated in the increased sensitivity to a multitude of external cues associated by conditioning to the threatening traumatic incident or incidents.

The symptoms of release, due to excessive activation of hindbrain centers, are the "constant" symptoms of the condition. These are the startle reaction (conditioned emotional response), irritability, hyperalertness, intrusive thinking, repetitive fearful nightmares and dreams of the event, and the various psychophysiologi-

cal expressions of the startle reaction or conditioned emotional response—expressed subjectively as palpitations, panic attacks, and other pains, including headache, nausea, vomiting, and diarrhea.

"Delay," intensification of symptoms, and dissociation may be recognized as expressions of primary cortical functional impairment. Each successive arousal of aggressive emotion by exposure to external stimuli or social incidents arousing the traumatic complex, if intense enough to overwhelm the central controls, leads to activation of the lower centers, which in turn reactivates the cortical areas related to emotions and memory. Highly intense arousal, as in terror, widely disrupts cognitive functioning and produces dissociative behaviors.

It is the inescapable recurrence of the physiological disturbance that affects personality organization and stability. The repeated reminders of the traumatic event associated with somatic symptoms disrupt the sufferer's body image and self-concept. Subsequent cognitive processing induces the reactive symptoms, which present as various avoidance behaviors and a chronic dysphoric-anxious state. Thus, one sees avoidance behaviors such as social withdrawal, distancing from others, alcohol and drug abuse, or compulsive activities (including work) and affective disturbances (depression, survival guilt, and shame with suicidal ideation). These symptoms cause diagnostic difficulty only when examiners fail to probe for the primary symptoms mentioned heretofore in this paper.

Additional intrapsychic attempts lead to restitutive symptoms and behaviors as the individual recognizes his deficiencies in social relations due to loss or fear of loss of control of aggressive behavior. In conflict, he musters up whatever personality resources and psychological defenses are available to him. The sufferers are often thought to have a personality disorder. Lindy and Titchener (26) emphasized that character change is to be expected after exposure to overwhelming personal disasters.

As for predisposition to develop the chronic form of posttraumatic stress disorder and its variable impairment of psychosocial functioning, I now classify all patients as having severe, moderate, or mild forms of the disorder. These classifications depend on the number of symptoms, their expression, and evidence of the conditioned emotional response as well as the potential for later intensification of symptom expression on re-exposure to emotional stress. If change has occurred through excessive stimulation, future processing of such messages will vary according to the extent of sensitizing change brought about by the excessive traumatic stimulation as well as the number of activated neurons available.

Younger persons are said to be more susceptible to the development of posttraumatic stress disorder. They have had less experience and therefore, perhaps, less neuronal activation. Older persons, who are also more susceptible, are already undergoing neuronal inactivation. As for the reported greater resistance of military

officers to developing posttraumatic stress disorder, we may presume that their neuronal network is numerically larger than that of nonofficers and, through education and diverse experiences, better evolved and integrated and therefore more flexible. Persons who have been emotionally traumatized early in life may be thought to be at risk for breakdown, depending on the intensity and duration of the early life-threatening experience. My clinical experience is that surviving men who developed symptoms on the combat line and were returned to duty only to collapse later have ended up with the most severe pathology—the "catetenoid" states. On the other hand, healthy soldiers who have been sensitized to exposure to emotional suffering by their near catastrophic experience often develop adaptive social behaviors; their capacity for empathic understanding often seems enlarged.

This neuropsychological hypothesis contains many implications for and already has influenced treatment planning and procedures (27). It has led to the trial of adrenergic blocking agents to attenuate the cardinal symptoms of the disorder (28).

#### POTENTIAL FUTURE RESEARCH

Is it possible through research to discover support for the hypothesis put forward? Some immediate projects come to mind:

- 1. Examine with modern imaging techniques the physiological and neurochemical processing of meaningful combat-simulating stimuli and nonmeaningful stimuli in combat-induced posttraumatic stress disorder victims and control groups.
- 2. Examine particularly the limbic and lower brainstem structures with modern neuropathological and neurochemical techniques in post-mortem material from combat veterans, concentration camp survivors, and former prisoners of war with posttraumatic stress disorder.
- 3. Examine prospectively psychophysiological, electrophysiological, and neurochemical responses in both baseline and arousal status in abused and nonabused children.
- 4. Carry out similar studies in animals with fear-conditioned chronic states.

#### REFERENCES

- 1. Kolb LC, Mutalipassi LR: The conditioned emotional response: a sub-class of the chronic and delayed post-traumatic stress disorder. Psychiatr Annals 1982; 12:979–987
- Blanchard EB, Kolb LC, Pallmeyer TP, et al: A psychophysiologic study of post traumatic stress disorder in Vietnam veterans. Psychiatr Q 1983; 54:220–228
- Blanchard EB, Kolb LC, Gerardi RJ, et al: Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post traumatic stress disorder in Vietnam veterans. Behavior Therapy 1986; 17:592–606
- Dobbs D, Wilson WP: Observations on persistence of war neurosis. Dis Nerv Syst 1960; 21:686-691

- Malloy PF, Fairbank JA, Keane TM: Validation of a multimethod assessment of post-traumatic stress disorders in Vietnam veterans. J Consult Clin Psychol 1983; 51:488–494
- Kolb LC: The post traumatic stress disorders of combat: a subgroup with a conditioned emotional response. Milit Med 1984; 149:237–243
- Wenger MA: Studies in Autonomic Balance in Army-Air Force Personnel: Comparative Psychological Monograph. Berkeley, University of California Press, 1948
- Mason J, Giller EL, Kosten TR, et al: Elevated norepinephrine/ cortisol ratio in PTSD, in New Research Program and Abstracts, 138th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1985
- Kardiner A, Spiegel H: The Traumatic Neuroses of War. New York, Paul Hoeber, 1947
- Anderson OD, Parmenter R: Long-Term Study of the Experimental Neurosis in the Sheep and Dog: With Nine Case Histories. Psychosomatic Medicine Monograph 2(3.4, 1941)
- Solomon RL, Wynne LC: Traumatic avoidance learning: the principles of anxiety conservation and partial irreversibility. Psychol Rev 1954; 61:353-385
- 12. Hubel DH, Wiesel TH: Ferrier lecture: functional architecture of macaque monkey visual cortex. Proc R Soc Lond [Biol] 1977; 198:1-59
- Kandel ER: Environmental determinants of brain architecture and of behavior: early experience and learning, in Principles of Neural Science. Edited by Kandel EP, Schwartz JH. New York, Elsevier/North Holland, 1982
- Reiser MF: Mind, Brain, Body: Toward a Convergence of Psychoanalysis and Neurobiology. New York, Basic Books, 1984
- Freud S: Beyond the pleasure principle (1920), ir Complete Psychological Works, standard ed, vol 20. London, Hogarth Press, 1959
- 16. Miller JG: Living Systems. New York, McGraw-Hill, 1978
- 17. Schuknecht H: Pathology of the Ear. Cambridge, Harvard University Press, 1974, pp 302-303
- 18. Miller JD: Effects of noise on people. J Acoust Soc Am 1974; 56:729-740
- 19. Freud S: Preface, in Psychoanalysis and the War Neuroses. By Ferenczi S, Abraham K, Simmel E, et al. New York, International Psychoanalytic Press, 1921
- Ferenczi S: Theory and Technique of Psychoanalysis. New York, Basic Books, 1952
- 21. Keane TM, Zimmering RT, Caddell JM: A behavioral formulation of post traumatic stress disorder in Vietnam veterans. Behavior Therapist 1985; 8:9–12
- 22. Jackson JH: Selected Writings, vol II: Evolution and Dissolution of the Nervous System. Edited by Taylor J. New York, Basic Books, 1958
- Sapolsky RM, Krey LC, McEwen BS: Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc Natl Acad Sci USA 1984; 81:6174–6177
- 24. Redmond DE: Alterations in the function of the nucleus locus coeruleus: a possible model for studies of anxiety. in Animal Models in Psychiatry and Neurology. Edited by Hanin I, Usdin E. Oxford, Penguin Press, 1977
- Hoppe KD, Bogen JE: Alexithymia in twelve commissurotomized patients. Psychother Psychosom 1977; 28:148–155
- Lindy JD, Titchener J: Acts of god and man: long term character change in survivors of disasters and the law. Behavioral Science and the Law 1983; 1:85–96
- Kolb LC: A theoretical model for planning treatment of post traumatic stress disorders of combat. Curr Psychiatr Ther 1986; 23:119-127
- 28. Kolb LC, Burris BC, Griffiths S: Propranolol and clonidine in treatment of post traumatic stress disorders, in Post-Traumatic Stress Disorder: Psychological and Biological Sequelae. Edited by van der Kolk BA. Washington, DC, American Psychiatric Press, 1984

#### The Theory and Practice of Movie Psychiatry

Irving Schneider, M.D.

The depiction of psychiatry in the movies has been a source of concern over the years to many in the profession who feel that a false picture of psychiatrists' work has been presented to the public. In fact, psychiatry in the movies has developed its own characteristics, which only occasionally intersect with those of the real-life profession. This paper outlines the methods and theories of the invented profession of movie psychiatry.

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E arly in the twentieth century, movie makers invented a new profession they called "psychiatry." Like its medical namesake, it began tentatively and cautiously, but as the years passed it developed a momentum and a confidence that made it the mainstay of a variety of film story lines and genres. From time to time the invented profession, through intent or coincidence, resembled the real profession of psychiatry, but for the most part it created its own nosology, treatment methods, theories, and practitioners.

The movies have invented other occupations—dentist, lawyer, cowboy, cops and robbers, priest—but psychiatry and the movies have demonstrated a special affinity for each other, since to an uncommon extent they share an interest in human behavior in general and deviations from the norm in particular. Movie stories and psychiatric case histories have always drawn their content from the same reservoir of heightened emotions and unusual motivations.

Of course, the depiction of the human drama does not require a psychiatrist. Throughout history, drama and biography have presented life histories and interpretations without benefit of an organized psychological system, and medicine has attempted to cope with aberrant behavior patterns without recourse to a separate specialty. At the dawn of the century, however, it became clear that there was a gap in the understanding, depiction, and treatment of pathological behavior which cried out for the invention of a new specialty, one that would meet the needs of both science and the humanities.

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Movies and modern psychiatry thrived with the new century and, within a very few years, began to take note of each other. Some psychiatrists, Kraepelin among them, expressed the hope that the filming of patients would aid in the understanding of their pathological states, and film makers hoped that psychological subject matter would help satisfy the public's almost insatiable demand for new film subjects.

The movies' linkage with psychiatry began not with the psychiatrist but with the depiction of a variety of patients: the hospital inmates dressed as Napoleon in The Escaped Lunatic and Maniac Chase of 1904, the homicidal Maniac Barber of 1902, The Kleptomaniac of 1905, the infanticidal Maniac Cook of 1909, and a host of early drunkards. In 1901 Georges Méliés made The Escapees From Charenton (released in Britain as Off to Bedlam and in the United States as Off to Bloomingdale Asylum), which turned out to be nothing more than a surrealistic minstrel show—a comment on the status at the time of both black people and mental patients.

The first movie psychiatrist made his appearance in 1906 in the form of the imposing but harried superintendent of *Dr. Dippy's Sanitarium*. Shortly afterward, in 1908, D. W. Griffith, who pioneered so many aspects of the movies, depicted the first private, outpatient psychiatrist in *The Criminal Hypnotist*. These films merit a close look, for in them the very first depictions of movie psychiatrists at work—the outlines of the invented profession—are already evident. We can already detect, in nascent form, many of the characteristic features of the profession that have persisted through movie history.

The Dr. Dippy film is mainly concerned with a young man whom the doctor hires as an attendant at the sanitarium. The new employee is introduced to the four patients who are to be in his care, one of whom is a woman; they perform comic lunatic routines and then begin to harass him. Finally, the three male patients chase him out of the hospital and into the country, closely followed by the corpulent Dr. Dippy and other attendants. As was characteristic of other maniac chase films, the chase ends back at the hospital, where the good doctor distracts and soothes the increasingly violent patients by giving each a pie (the first major tranquilizer in the movies?). The attendant decides to leave his job.

With The Criminal Hypnotist, a significant advance in movies clearly occurred. Instead of the primitive story and action of the earlier film, the plot was more developed, the acting less broad, and the emotions more complex. It opens with a party scene in which a young gentleman with a black beard is entertaining appreciative guests by hypnotizing several of them, including the hostess and her male friend, and inducing them to perform silly tasks. The following day, the young hostess encounters the hypnotist on the street. He immediately hypnotizes her and leads her into his apartment. Briefly considering a sexual pass, he turns quickly to more immediate business, instructing her to steal her father's money from the desk drawer in which he keeps it. In an obvious trance, she goes home and starts to take the money, but she cannot bring herself to complete the task. She returns to the hypnotist without the money, followed by her male friend, who is puzzled by her strange demeanor when he encounters her on the street. The hypnotist subdues and ties up the friend and then deepens the woman's trance and accompanies her to her father's room. He takes the money himself and leaves her behind. When the father enters the room, he finds his daughter in a strange state and sends for a doctor. The puzzled doctor throws up his hands and instructs the maid to fetch a specialist. The next scene shows the maid entering a house with a shingle on it that identifies the occupant as a "mind specialist," an appellation apparently more meaningful to audiences of the day than the term "psychiatrist" or "alienist." The large, stocky, bearded specialist, who is seen with his male secretary or nurse, quickly follows the maid to the troubled household. He immediately recognizes the problem and lightens the trance, preserving enough of it to enable the young woman to lead the two doctors, the father, and a policeman to the hypnotist's lair. As the policeman frees the imprisoned friend and takes the villain away, the "mind specialist" fully clears the young woman's mind, and she falls happily into her father's embrace.

What we see in these films is the emergence, when we include the hypnotist, of three distinctly different kinds of mental experts. In another paper (1) I have called them Dr. Dippy, Dr. Wonderful, and Dr. Evil. Each type, as it has evolved in movie history, has differentiated into a distinct pattern of practice.

#### THREE TYPES OF MOVIE PSYCHIATRISTS

Hollingshead and Redlich (2), in their study of social class and mental illness, delineated two types of psychiatrists—the directive-organic and the analytical-psychological—and described the differences in their career patterns. The two types tend to see different kinds of patients, use different treatment methods, and operate from different theoretical positions. Similarly, the three kinds of movie practitioners differ in theory, method, and patients treated.

Dr. Dippy is the familiar comical movie psychiatrist—the one who is crazier or more foolish than his patients. When his patients are crazy, they are likely to

be comically so, but more often than not they are either not really sick or, despite their illness, wiser than the doctor. Whatever theory Dr. Dippy uses, in his hands it lacks or defies common sense. His treatment methods tend to be bizarre, impractical, or unusual. Fortunately, they seldom do any harm. Some of the better-known doctors in this category are Wyrley Birch, the Dr. Von Haller of Mr. Deeds Goes to Town (1936), who condemns Mr. Deeds but is himself exposed as a fool; Fritz Feld in Bringing Up Baby (1938); Fred Astaire in Carefree (1938); and more recently, Peter Sellers in What's New, Pussycat? (1965); Mel Brooks in High Anxiety (1977); Richard Benjamin in Love at First Bite (1979); and Peter Bonerz in Serial (1980).

Dr. Wonderful was a more recent arrival on the movie scene. Perhaps because few film makers had any real experience with psychiatry before the late 1930s and early 1940s, or because of the obvious difficulty in depicting the talking cure in the age of silent movies, the dramatically successful presentation of the work of psychiatry, with few exceptions, had to wait for the 1940s. However, once Dr. Wonderful appeared on the scene, there was an avalanche of films depicting his work.

As he evolved, several aspects of Dr. Wonderful's career pattern became increasingly clear. To begin with, he is invariably warm, humane, modest, and caring. Time is of no concern to him. He does not seem to work by the clock, and, in fact, patients can see him or talk to him at any time and for any length of time. This is dramatically demonstrated in the 1983 Lovesick, in which Dudley Moore scraps his psychoanalytic practice and goes out to work with sick, poor, and needy patients. As an ineffectual, bored, officebound psychoanalytic Dr. Dippy, his life is entirely governed by the clock, which figures prominently in the scenes depicting him at work, but as soon as he becomes a Dr. Wonderful, he is available at all hours and in all places. This availability was prefigured in Dr. Wonderful's first incarnation in The Criminal Hypnotist, when he rushed out of his office and into the patient's home at a moment's notice to perform his good works.

In his treatment, Dr. Wonderful is especially skillful at improvisation, coming up with the appropriate, if often unorthodox, maneuver or interpretation at just the right time. This is especially useful in that favorite movie device, the uncovering of the traumatic event—the royal road to the instantaneous cure. Again, The Criminal Hypnotist is the prototype and Ordinary People (1980) the more recent example.

Like Hollingshead and Redlich's analytical-psychological therapist, Dr. Wonderful eschews coercive treatments. ECT, lobotomy, and heavy use of psychotropic drugs are not in his armamentarium. Occasionally, he will use hypnosis or truth serum, but only in a deeply caring manner—never manipulatively. His chief method is the talking cure, in which both patient and doctor share the talking.

The third of the movie types is Dr. Evil. He is a familiar figure in the history of horror movies and, in fact, had his first striking appearance in that early triumph of horror films, *The Cabinet of Dr. Caligari* (1919). Despite the tricky reversal at the end of the film, Dr. Caligari is the model for the psychiatrist who becomes evil because he dabbles in forbidden, dangerous areas of experimentation. He is the Dr. Frankenstein of the mind, using others to achieve his goals and unleashing evil on the world. Examples abound in screen history.

Another Dr. Evil is the psychiatrist who uses his powers for personal profit. From *The Criminal Hypnotist* to *Nightmare Alley* (1947) to *Shock Treatment* (1964) to *I, the Jury* (1982) and beyond, we have seen a line of psychiatrists who have attempted, by using authority or skill, to bilk patients of their money.

The last subtype of Dr. Evil is the psychiatrist who is sufficiently mad, neurotic, or insecure to abuse his profession and perform evil deeds. The most egregious example, outside the exploitation film genre, is the doctor played by Michael Caine in *Dressed to Kill* (1980), a psychiatrist who when sexually aroused becomes a homicidal, transvestite amnesiac. Another famous homicidal psychiatrist is played by Leo G. Carroll in the landmark psychiatric film *Spellbound* (1945). Somewhat more controlled practitioners of this ilk appear in *Frances* (1982) and *One Flew Over the Cuckoo's Nest* (1975).

The chief characteristic of Dr. Evil, whatever his nature or intent, is his willingness to use what have been viewed as the coercive tools available to psychiatry. These include commitment of patients to an institution, experimentation, ECT, lobotomy, heavy medication, and hypnosis. In his hands these become tools for control, manipulation, power, revenge, and financial gain, and in the movie public's mind these methods have all become associated with nefarious pursuits. Apart from a few successful uses of hypnotism in the treatment of dissociative states and one course of ECT in *Fear Strikes Out* (1957), it is hard to find examples of a sympathetic presentation of these forms of treatment.

In a review of 207 American films depicting psychiatrists, exclusive of exploitation and horror films, I calculated the prevalence of each type of psychiatrist I have described. Throughout the history of American movie psychiatry, 35% of the practitioners have been Dr. Dippys, 15% Dr. Evils, 22% Dr. Wonderfuls, 14% unclassifiable, 9% hapless or inept but not easily typed, and 5% effective but not easily typed. If the exploitation movies were included, the percentage of Dr. Evils certainly would increase sharply. This is not a flattering distribution of therapists; we can speculate on the course of a real profession if only 27% of its practitioners were judged to be effective and up to 20% downright cruel or dangerous.

By now, some readers may protest that beginning with the Dr. Evil in *The Criminal Hypnotist*, who is perhaps nothing more than a party hypnotist, not all

the movie psychiatrists I have cited are really psychiatrists. But by including mind experts, psychologists, psychoanalysts, social workers, lay therapists, and quacks under the same heading, I am merely following movie convention. The movies have never been scrupulous in their bestowal of professional titles and functions on the variety of mind workers they have depicted. In an early example, the evil mind worker in When the Clouds Roll By (1919), who attempts to drive Douglas Fairbanks, Sr., to suicide, is first seen lecturing to a large medical audience in an amphitheater but is later unmasked as an escapee from the New York Insane Asylum. In a more recent example, Peter Bonerz in Serial (1980) is a psychologist who freely prescribes and dispenses medication.

One might think that these depictions stem from ignorance, but that does not appear to be the case. In the first version of The Dark Mirror (1946), Lew Ayres is presented as Dr. Scott Elliott, M.D., Psychologist. He is a physician who administers the Rorschach test to his patient. When the film was remade for television in 1984, Dr. Elliott was transformed into a psychology professor at a university but is introduced as a psychiatrist! One is forced to conclude that the confusion arises because in movie psychiatry distinctions are not important. One surprising exception to this rule occurs in Miracle on 34th Street, in which Edmund Gwenn as Kris Kringle berates his nemesis psychologist for practicing psychiatry; otherwise, in the movies, a mind expert is a mind expert, and the preferred generic term is "psychiatrist."

#### PSYCHOANALYSIS IN THE MOVIES

Still, the movies have at times sought to distinguish between generic psychiatry and the subspecialty of psychoanalysis—a distinction that seemed more important to the industry in the 1930s and 1940s. Farber and Green (3) have suggested that this emphasis stemmed in part from the key position of psychoanalysis in the life of many prominent Hollywood families. The three major distinctive aspects of psychoanalysis that emerged in the movies of the period were the presence of an unconscious or subconscious mind, the importance of dream analysis, and an interest in love as the prime human emotion.

Here is how psychoanalyst Fred Astaire explains his profession to reluctant patient Ginger Rogers in *Carefree* (1938):

"Miss Cooper, you understand the principle of psychoanalysis, don't you? ... You do know that you have two minds, the conscious and the subconscious? The conscious mind is the ego; that's the thing that says 'I am I and you are you.' ... Let me put it this way. [Hand to back of head] Back here is a jungle full of the most noble and horrible things.... That's your subconscious mind. It works all the time, even when you sleep. It dreams. It never forgets anything. Your conscious mind lies here. [Hand to front of head] It doesn't dream. It thinks. What we try for

is perfect coordination between the two. Do you understand?"

"No. I don't believe I care to. When I first came in here I wasn't sure I wanted to be psychoanalyzed. Now I'm positive I don't."

"Now you mustn't put a wall between us. To psychoanalyze you I have to interpret your dreams. What sort of things do you dream?"

"I don't dream."

"Oh, come now, everybody dreams. . . . I wish you'd please understand that I'm only trying to help you find

"Well, if I ever get lost I'll call on you."

This, then, is a sample of *ur*-psychoanalysis in the movies. By 1945, when Spellbound was made, the industry had grown more sophisticated. The producer, David Selznick, had had some personal analysis; his analyst, May Romm, was a consultant to the film; and the screenwriter, Ben Hecht, had done his homework interviewing several analysts. Here is how European analyst Michael Chekhov explains his work to amnesic patient Gregory Peck:

I'll explain to you about dreams so you don't think it is hooey. The secret of who you are and what has made you run away from yourself-these secrets are buried in your brain, but you don't want to look at them. The human being very often doesn't want to know the truth about himself because he thinks it will make him sick; so he makes himself sicker trying to forget. You follow me? . . . Here's where dreams come in. They tell you what you are trying to hide, but they tell it to you all mixed up like pieces of a puzzle that don't fit. The problem of the analyst is to examine this puzzle and put the pieces together in the right place and find out what the devil you are trying to say to yourself.

What Spellbound accomplished, as revealed in this exegesis, was to establish a link between the methods of criminal detection and the psychoanalytic method. In both endeavors, clues are pursued to solve a mystery. The truth of an event is buried beneath an accumulation of alibis, subterfuges, false tracks, confusing recollections, and the like, and the analystdetective patiently digs and deduces until the solution suddenly appears. Throughout movie history, the psychoanalyst has been a solver of mysteries—often criminal ones, as in Spellbound, but just as often personal

The last movie analytic concept, the connection between psychoanalysis and love, came early. It was reported in 1925 that Samuel Goldwyn had offered Freud \$100,000 to cooperate in making a film depicting scenes from famous love stories of history. Freud turned down the offer but was amused at the popular connection between psychoanalysis and love, a connection that may then have been based on ignorance. However, as the censorship power of the Hays Office and the Production Code grew and the word "sex" became taboo, love became in the movies both a euphemism and a form of sublimation for the more profane word and impulse.

An early example of the substitution of love for sex occurs in Conflict (1945), in which Sydney Greenstreet plays a crime-solving therapist. In the following scene, killer-to-be Humphrey Bogart and his soon-tobe-murdered wife speak to the therapist about his work:

"Just what kind of doctor are you?"

"I deal with thoughts and dreams which no amount of surgery can handle. You see, sometimes a thought can be like a malignant disease that starts to eat away the will power. When that happens it is my business to remove the thought before it can cause destruction."

"... What do you eminent psychoanalysts think causes these thoughts, doctor?"

"Oh, any number of ... things, but I should say love and its frustrations is the worst offender."

"You see, Dr. Hamilton belongs to the Freudian school of psychology that believes love rather than money is the root of all evil."

#### INFLUENCE OF EUROPEAN PSYCHIATRY

Sydney Greenstreet mentions later in the same movie that he was trained in Vienna, and in this disclosure he reveals himself to be very much a part of the first generation of movie psychiatrists. Screen psychiatrists of the 1930s and early 1940s, like their real-life psychiatric colleagues, often saw the Austrian capital and other Central European cities as the mecca for their profession. Robert Cummings, Ronald Reagan's buddy in Kings Row (1941), is a prominent example of a sensitive American youth who travels to Vienna to learn the new psychiatry. Pilgrimages were not made in only one direction, however, for at the same time, Middle Europeans, often bearded, were finding themselves practicing in American movie locations. Both kinds of pilgrimages resulted in increased sophistication in movie psychiatry.

It was European psychiatrist Charles Boyer who introduced Continental knowledge and understanding in Private Worlds (1936), the first American movie to portray psychiatry seriously and to portray it from an Adlerian perspective. Ingrid Bergman, in *Spellbound*, learned her profession from a wise European mentor. There were exceptions, of course—notably, the foolish Viennese expert in Mr. Deeds Goes to Town—but for the most part there was a reverential connection between American film psychiatry and imagined European psychiatry.

It was not only psychoanalysis that the first generation studied in Europe. More often than not, movie psychiatrists in the 1930s wore white coats, struggled to find a serum for treating psychosis, and were prepared to treat physical illness and even do surgery when necessary. Their offices were equipped with skeletons, white cabinets, and medical charts and instruments; nurses abounded. Their psychiatric coming of age in the films of the period occurred when they learned to regard patients as human beings as well as bodies upon which to work their tests (*Private Worlds* [1936], *The Amazing Dr. Clitterhouse* [1938], *Shining Victory* [1941], *Condemned Women* [1938]).

#### MODERN MOVIE PSYCHIATRY

It was not until the 1940s that modern movie psychiatry began to emerge, but by the end of that decade it had become codified to such an extent that it has been little changed since. The nosology, the main treatment methods, and the explanatory theories have remained essentially the same as those laid down by the practitioners of the period, and the case histories presented in films of the era remain the classic statements of movie psychiatry. Consider Now Voyager (1942), Lady in the Dark (1944), Spellbound (1945), The Dark Mirror (1946), Let There Be Light (1946), Possessed (1947), The Snake Pit (1948), and Home of the Brave (1949). These memorable films, among the many psychiatric films of the time, contain within themselves most of the elements still characteristic of present-day psychiatric films.

#### Favorite Movie Diagnoses

The movie diagnostic manual has been little revised over the years. Its main categories have remained consistent and quite different in nature and emphasis from those of DSM-III. Combining movie and DSM-III nomenclature, the list of disorders overrepresented in the movie manual are the following: dissociative reaction, especially amnesia and multiple personality; homicidal mania; substance abuse; disorders of impulse control; hysterical paralysis; phobic disorders; transsexualism and transvestism; factitious disorder, usually with psychological symptoms; schizophrenic and paranoid disorders; and no mental illness, with or without greater wisdom.

One of the most important movie diagnoses through time has been amnesia. Its importance to the development of film stories cannot be overestimated, nor can its affinity for the most interesting and innovative treatment methods. The classic example of its plot possibilities occurs in *Spellbound*, where Gregory Peck's total amnesia is cured by Ingrid Bergman. More typically, however, it is a woman who is suffering from this malady—Joan Crawford in *Possessed*, for example—and all the skills and ingenuity of her sympathetic male therapist are needed to reach that inevitable outcome, the uncovering of the traumatic event. Once this has been achieved, the amnesia disappears and all ends well.

Related to amnesia, and also overrepresented in the cinematic diagnostic manual, is the most spectacular of dissociative reactions, the multiple personality. Its presentation on the screen has usually combined bravura performance and dramatic reenactments of past events with fine detective work. The best-known examples are *The Three Faces of Eve* (1957) and *Sybil* 

(1976), both featuring Joanne Woodward, first as patient, then as therapist; but two other prominent films in this category demonstrate the many axes that movie diagnoses can occupy. *Psycho* (1960) and *Dressed to Kill* (1980) each present the case of a man with dual personalities; in one of his personalities he is pleasant and sympathetic, but in the other he dresses as a woman and commits horrible murders. In that one person three common movie diagnostic categories merge: dissociative reaction, homicidal mania, and transsexualism and transvestism.

It is hard to imagine where the horror film—that most rooted of movie genres—would be without the psychiatric case book. Indeed, as noted earlier, the earliest internationally acclaimed horror film, The Cabinet of Dr. Caligari (1919), was also the first prominent film about a psychiatrist. Every category in the movie diagnostic manual turns up in accounting for the behavior of the horror film protagonist, but easily the most prominent symptom is homicide, and the most common diagnosis, homicidal mania. To explain the affliction—and horror films almost always attempt to explain-a limited number of different etiologies have been offered: genetics; possession by aliens, spirits, or the devil himself; schizophrenic or paranoid disorder; child abuse; and, surprisingly frequently, witnessing as a child a grisly crime. When homicidal mania appears in another genre, the crime or detective film, the behavior tends not to be explained or, more often than not, is attributed to sociopathy.

Alcoholism, drug abuse, pathological gambling, kleptomania, and explosive behavior have all been the subject of a number of fine films and require no elaboration. Hysterical paralysis has tended to appear most often in war films. John Huston's long-suppressed Let There Be Light (1946) is the classic presentation of the illness and its treatment by narcosynthesis, but the most famous fictional depiction occurs in Home of the Brave (1949), the first successful modern film on race.

Transsexualism and transvestism have already been alluded to in their multiple personality manifestation, but, in fact, cross-dressing has been a cinema staple from the very beginning of movie history (4): Most often it has appeared in comedies, with no mental illness implied, but a number of films have treated it as an element of emotional disturbance. The most bizarre depiction of the problem appeared in *Glen or Glenda* (1953), directed by Ed Wood, an ex-Marine who allegedly wore women's underwear under his ordinary male garb.

Phobic disorders have appeared with almost the same frequency in comic movie psychiatric practice as in serious films. The split distribution parallels the public view of this unfortunate condition; there are as many jokes about agoraphobia as there are expressions of concern. The split is strikingly demonstrated in the contrast between the dramatic use of acrophobia in the Hitchcock film *Vertigo* (1958) and its comic use

in Mel Brooks's parody of that film, High Anxiety (1977).

Another split occurs in the movie treatment of schizophrenia and paranoid disorders, but here the division is between serious films and exploitation horror films. The serious films about psychosis—The Snake Pit (1948), David and Lisa (1962), I Never Promised You a Rose Garden (1977)—have been far outnumbered by the depictions of psychotic behavior in the schlock genres, where sensationalism or titillation rules.

The treatment of the factitious disorders has been the province of the Dr. Dippys of the movies. As the nomenclature indicates, the typical story is about a patient who manufactures concerns and problems in order to be in treatment with an idealized therapist. Given the sexual politics of the movies and of the society they mirror, the patient is usually female and the Dr. Dippy is, unsurprisingly, a male psychoanalyst. (For the career patterns of female therapists in the movies, see Schneider [5] and Samuels [6].) A telling example occurs in Oh Men! Oh Women! (1957). As psychoanalyst David Niven (who has struggled to stay awake during his matronly patient's recital of her dreams) helps his patient into her fur wrap at the end of the session, he engages in the following dialogue in response to her gushing comment that her psychoanalyst is like a god.

"A psychoanalyst is simply a doctor who is trained in the complexities of human behavior, and it is his business to try to bring about some harmony between the intellect and the emotions."

"Oh, you have for me, doctor. Before I came to you, you have no idea how dull my dreams were. . . . I wasn't even in some of them."

In Marshall Brickman's Lovesick (1983), a wicked satire of the world of psychoanalysis, another matron speaks from the couch:

"It's more like, Who am I really? Who am I? Am I wife, Mrs. Irwin Mondragon of New York City and Great Neck? Or am I mother, daughter, travel agent? Or am I merely, perhaps, patient? Your patient. What do you think?"

The audience and psychoanalyst Dudley Moore are saved from a response by the clock signaling an end to the session.

A common public perception of psychotherapy is clearly reflected in the depiction of factitious disorders. Many people believe that individuals who go to a psychiatrist are merely indulging themselves in what is no more than one element of a certain modern life style. The notion that the therapist is simply a replacement for a minister, a confidant, or a lover is heard all too often and is an element in the debate over third-party payments for psychiatric treatment. To the extent that real psychic pain or illness or both are denied, the legitimacy of psychiatry as a profession is undermined.

The Well Patient

A related attack on the profession occurs in the presentation of the last element in the movie diagnostic manual that I shall discuss: no mental illness, with or without greater wisdom. This category has appeared most often in films that attack the pretensions or authority of psychiatry, both as a profession and as the agent of a repressive society. The "patient" is presented as an ordinary citizen who has somehow fallen into the clutches of a movie psychiatrist or as an exceptional person, a rebel against conventional society, whose special qualities elude the rigid, hidebound psychiatrist. The movie argument for the nonconforming patient is presented by poet Sean Connery in A Fine Madness (1966) when he tells the psychiatrist, "You protect what is; I envision what can be."

A frequent plot in this category concerns innocent victims of manipulation or misunderstanding who are committed to a mental hospital and then have a terrible time convincing the authorities that they are sane. Sometimes they succeed, as in *Harvey* (1950) and *The Shrike* (1955), but sometimes they fail, often with tragic consequences, as in *Frances* (1982), the purportedly true story of movie star Frances Farmer, who endured unspeakable humiliations and a lobotomy during a series of hospital commitments, and *One Flew Over the Cuckoo's Nest* (1975), in which the fictional hero endures humiliations and a lobotomy.

In another version of the well-patient story, the action centers on a judicial hearing or some official examination during which a pompous psychiatrist makes a fool of himself in attempting to diagnose a normal or gifted hero. Mr. Deeds Goes to Town is the classic example.

Paul Mazursky and Woody Allen are two film makers who have explored in a series of films, mostly comedies, the gray area between the more serious mental disorders and the psychopathology of everyday life. In their works audiences have had difficulty distinguishing between real pain and self-indulgence, between the need for therapy and an addiction to therapy. In portraying the psychiatric profession, both men have drawn on their own personal experience with therapy to achieve a sense of authenticity. Mazursky has attained even greater verisimilitude by casting real therapists as movie therapists: psychiatrist Donald Muhich in Bob and Carol and Ted and Alice (1969), Blume in Love (1973), and Willie and Phil (1980) and psychologist Penelope Russianoff in An Unmarried Woman (1978). The progression in Muhich's roles may reflect Mazursky's growing disillusionment, for in his first two appearances Muhich slyly but competently treats people experiencing real discomfort, but in Willie and Phil he is an odd Draft Board psychiatrist who is fooled by the hero's malingering, and, finally, in Down and Out in Beverly Hills (1986) he appears as a psychiatrist for dogs. We can only wonder if Mazursky sees psychiatry itself going to the dogs.

#### PSYCHIATRY IN THE MOVIES TODAY

All is not lost on the movie front, however. The pessimism and sarcasm so prominent in recent portrayals of the profession are more than balanced by the enormously successful and inspiring Ordinary People (1980), the story of a teen-ager who returns to his suburban Chicago home after a stay at a mental hospital. The boy had made a serious suicide attempt after a boating accident, which he had survived but in which his older brother had drowned. He has trouble adjusting to school, friends, the stigma of hospitalization, and his mother's anger that the wrong son survived. With his father's encouragement and his mother's opposition, he begins to see a psychiatrist, who with understanding, insight, and warm support restores him to an effective and well-adjusted life.

In the course of the boy's treatment, depicted in great detail in the movie, the audience is introduced to almost every aspect of the work of the good movie psychiatrist—in fact, one of the most wonderful of all Dr. Wonderfuls. A review of the manners and methods of psychiatrist Dr. Berger, as portrayed by Judd Hirsch, will cap this story of movie psychiatry.

Within 30 seconds of the time Timothy Hutton, as Conrad Jarrett, pushes the buzzer at a door in an aging office building and Dr. Berger pops out from behind another, frosted glass door to motion him in, we learn a great deal about how the good movie psychiatrist works. The first thing that strikes us is that the doctor is casual and informal. He is wearing a sweater and corduroy pants, his collar and tie are loose, his hair is mussed, and he drinks coffee and smokes cigarettes while working. The appearance of his office reinforces the first impression. Nowhere can the hand of a decorator be discerned; the furniture could have been acquired from a secondhand furniture store. As the doctor moves about, it becomes obvious that he is no technocrat. In fact, he is casually clumsy in his handling of his answering machine and radio. What all of this strongly communicates, even before the session begins, is that the good movie doctor is not interested in status, money, or possessions.

As the opening session proceeds, we learn that, unlike the stereotypic psychiatrist, Dr. Berger talks. He leads, responds, admits mistakes, and appears to be a straight shooter, though a shrewd one. He clearly knows what is going on but waits for the appropriate time to share his knowledge. He is on the side of feelings, not control, but is firm and knows how to set limits.

In subsequent scenes we learn even more about the doctor's practice. In his office there is no fixed seating pattern; he and his patient change seats and freely walk around. He is reluctant to use medication, although not unalterably opposed to it, and he is interested in dreams but gives priority to real-life events. He is a realist in dealing with family events but is not antiparent. And finally, he is actively engaged with his patient, often with quick, spontaneous role playing.

The climactic therapy scene, an emergency nighttime one, involves the classic cure through abreaction to a past traumatic event reexperienced in the presence of the therapist. The significant insight, which has occurred in other movies, is that the central conflict is due not to the shock of the event but to survivor guilt. The scene ends with the patient tearfully embracing his therapist, who has assured him that he is his friend.

After decades of concern about the distorted picture of psychiatry being presented to the public by the movie industry and frequent suggestions that psychiatric consultants be used by the mass media, Ordinary People was greeted by psychiatrists with nearly universal relief, praise, and approbation. Overlooked in the response was the fact that much in the therapist's approach to his patient is contrary to the way many of us work. In fact, some things—the embrace between patient and therapist, for example—would be seriously questioned in peer review. The most significant aspect of the movie for therapists, then, is that it is a message about what the public wants the good psychiatrist to be and, judging from the profession's response, what good psychiatrists want to be.

It has always been clear that there is much for the movies to learn about real psychiatry. What has been ignored is that there is much for psychiatry to learn from its movie counterpart. When recommending hospitalization or assertive treatments, for example, the psychiatrist might well remember with what fear and distrust they are typically depicted in the movies. More important, the recurrent movie image of the good psychiatrist as the good parent—someone motivated by caring and not money, someone who works in a modest personal environment and is not reluctant to show concern and nonsexual affection, a person who is not bound by rigid rules or the inflexible clockshould not be dismissed as principally a transference phenomenon but be seen as the expression of a public desire psychiatry should heed.

Throughout the century psychiatry has sought scientific understanding and effective treatment for the conditions so vividly depicted in the movies. At the same time, movie psychiatry has projected a view of the profession through the distorting lenses of fear, defensive ridicule, and the yearning for an ideal parent. To the extent that the parallel professions pay attention to each other's work, both may profit.

#### REFERENCES

- Schneider I: The psychiatrist in the movies: the first fifty years, in The Psychoanalytic Study of Literature. Edited by Reppen J, Charney M. Hillsdale, NJ, Analytic Press, 1985
- Hollingshead AB, Redlich FC: Social Class and Mental Illnéss: A Community Study. New York, John Wiley & Sons, 1958
- Farber S, Green M: Hollywood Dynasties. New York, Ballantine Books, 1985
- Dickens H: What a Drag: Men as Women and Women as Men in the Movies. New York, Quill, 1984
- 5. Schneider I: Images of the mind: psychiatry in the commercial film. Am J Psychiatry 1977;134:613-620
- 6. Samuels L: Female psychotherapists as portrayed in film, fiction and nonfiction. J Am Acad Psychoanal 1985;13:367–368

# Genetic Contributions to Human Fatness: An Adoption Study

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A strong relationship was found between the degree of fatness of biologic mothers and that of their adult offspring who had been separated from their mothers at birth and adopted during the first year of life. This relationship persisted even after age, height, and possible confounding environmental factors were controlled. There was little evidence for either selective placement on the basis of parental fatness or gene-environment interaction. There was no relationship between the degree of fatness of adoptive parents and that of the adoptees. Two indexes of environmental influence—rural upbringing and disturbance in the adoptive home—predicted fatness among adoptees.

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H uman fatness is familial. Most offspring of overweight parents are overweight; most offspring of lean parents are lean (1). Several family studies have

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shown that having an obese first-degree relative substantially increases an individual's risk for becoming obese (1–3). Five twin studies (4–9) have suggested that genetic factors play a large part in the familial transmission of fatness.

The study of adoptees is another method of assessing genetic influences in humans. With early, unselective placement the relationship between biologic parents and their adopted-away offspring provides a measure of genetic influence, while the relationship of adoptive parents and their adopted children indicates environmental influence. Three early adoption studies of human fatness found a stronger correlation of parents with their own biologic children than with children they had adopted (10–12); in one study the correlations were higher with adopted than with biologic children (13); and in another study the correlations of adoptive parents with their biologic and adopted children were about equal (14). These early studies were handicapped by the fact that none contained information about the biologic parents of the adoptee and in two studies (13, 14) stepchildren were included among adoptees. The inclusion of stepchildren may erroneously inflate the correlation of adoptees with their adoptive parents (15) because spouses tend to be correlated in levels of fatness. A third problem was that the adoptees in three of the studies were children (10, 11, 14), which limits the generality of the results, since obesity is a disorder with onset largely in adult life.

Information about biologic parents and adult adoptees was available for a recent study in which body mass index served as a measure of fatness (16). That study, conducted in Denmark, found a strong relationship between adoptees and their biologic parents and no relationship between adoptees and their adoptive parents.

We report here the second adoption study to obtain

information about biologic parents and the third in which the adoptees were adults. It is, to our knowledge, the first adoption study to assess the contribution of two environmental factors—rural versus urban upbringing and disturbance in the rearing home environment. The results of this study of Iowans substantiate the results of the recent adoption study of Danes (16).

#### **METHOD**

Adult adoptees (age 18 to 38 years) were identified through two Iowa adoption agencies: Iowa Children's and Family Services and Lutheran Social Services. Adoptees had been separated at birth from their biologic parents. Half had been originally selected for study because of an adoption agency record of psychopathology in their biologic families (17–20); the other half, without a record of psychopathology, were matched by age and sex to those with such records. Height, weight, and obesity or its absence played no part in selection of the adoptees, and no relationship was found between measures of adoptee fatness and psychopathology in biologic parents (see Results).

Information about adoptees and adoptive parents was obtained by interview with each adoptee and one adoptive parent. Height and weight of both adoptive and biologic parents were reported rather than measured. One of the adoptive parents (usually the mother) provided a self-report, as well as a report on her or his spouse. Adoptees reported on themselves. Height and weight of the adoptees and adoptive parents were reported at the time of the interview. Height and weight of the biologic parents were obtained from adoption agency records made at the time of adoption.

Self-reported height and weight were used in this study, since direct measurements of the adoptees and their parents were not available. A previous study by Stunkard and Albaum (21) on the accuracy of reported height and weight, involving eight sites with 1,300 subjects, revealed that self-reported height and weight corresponded closely to measured height and weight. Similar results have been found in five further studies (22–26).

Table 1 presents data on characteristics of the adoptees and their biologic and adoptive parents. Information on height and weight was available on 357 adoptees.

The measure of fatness used in this study was the body mass index (weight in kilograms divided by the square of the height in meters). The index is designed to provide a measure of fatness that is independent of height, and in our study this goal was realized. Correlations between body mass index and height were low (-0.17 to 0.10), and correlations with weight were high (0.78 to 0.91). We also analyzed the data by replacing the value (2.0) for the exponent of height in the computation of body mass index with an optimal value based on Benn's method (27) and found only trivial differences in results.

TABLE 1. Characteristics of Adoptees and Their Biologic and Adoptive Parents

		Age (years)		Bod Mar Inde	ss	Heig (cm		Weight (kg)		
Subjects	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Adoptees										
Daughters	172	23.8	5.8	22.4	3.7	165.8	8.0	61.4	11.0	
Sons	185	24.7	6.0	24.8	3.8	178.6	7.6	79.2	12.9	
Biologic parents										
Mothers	237	21.9	5.7	22.1	3.4	162.8	6.9	58.9	10.9	
Fathers	131	25.6	6.9	23.7	2.4	177.0	6.8	74.4	9.3	
Adoptive parents										
Mothers	334	53.6	9.5	24.2	3.8	164.2	5.8	65.3	11.1	
Fathers	317	54.4	9.3	25.5	3.0	178.4	6.8	81.2	10.3	

<sup>&</sup>lt;sup>a</sup>Body mass index=weight in kilograms divided by the square of the height in meters.

Since age was positively correlated with body mass index in most subgroups of this sample (0.01 to 0.31), a residual of the index regressed on age was computed separately for male adoptees, female adoptees, adoptive mothers, adoptive fathers, biologic mothers, and biologic fathers. The relationship between the body mass index of adoptees and of biologic and adoptive parents was examined by both correlation and regression analyses. We calculated Pearson product-moment correlations for residual body mass indexes with age regressed out between adoptee and both sets of parents. All available observations were used for each correlation.

In addition, hierarchical multiple regression analyses were performed to test for specific environmental effects, to remove possible confounds such as selective placement, and to test for possible gene-environment interactions. Environmental variables included adoptive parents' body mass indexes and two additional factors: rural (population of 2,500 or less) versus urban upbringing and a disturbed rearing environment. Included under disturbed rearing environment were several variables that could have adverse effects on the child—psychopathology, alcoholism, or drug abuse among adoptive relatives or death or divorce of the adoptive parents (which usually meant a single-parent family).

In carrying out regression analyses, we used an order of entry of predictor variables that was conservative with respect to a genetic hypothesis by entering first the environmental variables. In the first step of the hierarchical regression analyses, the dependent variable was the residual of the adoptee's body mass index with age regressed out. The residual body mass indexes of the adoptive mother and father, with age regressed out, were entered in step 1 to control for possible environmental effects represented by the indexes of these parenting figures as well as for any effects due to selective placement. Rural versus urban upbringing and a disturbed rearing environment were also entered in step 1. Step 2 included all possible multiplicative two-way interactions among the four environmental

TABLE 2. Correlation of Residual Body Mass Index<sup>a</sup> in Adoptees and Their Biologic and Adoptive Parents

	Ad	optee	Biologi	c Mother	Biolo	gic Father	Adoptive Mothe		
Relatives	N	r <sup>b</sup>	N	r <sup>b</sup>	N	, r <sup>b</sup>	N	r <sup>b</sup>	
Daughters									
Biologic mother	123	0.40 <sup>c</sup>							
Biologic father	62	0.18	60	0.05					
Adoptive mother	161	0.06	117	0.08	58	$0.27^{d}$			
Adoptive father	153	0.09	115	0.04	55	-0.08	147	$0.25^{e}$	
Sons									
Biologic mother	114	0.15							
Biologic father	69	0.08	62	0.07					
Adoptive mother	173	0.04	110	0.05	63	0.15			
Adoptive father	164	-0.09	103	-0.09	61	0.08	154	0.07	

<sup>&</sup>lt;sup>a</sup>Body mass index=weight in kilograms divided by the square of the height in meters.

variables. Variables in each step were forced into the regression equation, regardless of their predictive val-

The biologic mother and father's body mass indexes, with age regressed out, were entered in step 3. Step 4 included all possible multiplicative two-way interactions between "genetic" variables (the biologic parents' body mass indexes) and the environmental variables (the adoptive parents' body mass indexes, rural versus urban living, and disturbance in the rearing environment). This step assessed the importance of gene-environment interactions, i.e., the extent to which the expression of a biologic predisposition depends on the environment in which the individual develops. The dependent variable in steps 2 through 4 was the residual calculated from the previous step, thereby removing the effects of the independent variables in all previous steps.

The hierarchical regression analyses used two overlapping subsets of data—samples A and B. Subsetting the data was undertaken to control for missing data on biologic fathers. Sample A consisted of 301 families with information about adoptee and both adoptive parents. Sample A contained information on 209 biologic mothers. Sample B used all interviewed adoptees for whom age, height, and weight were recorded; missing information on the body mass index of parents was replaced by appropriate group index means, computed within sex and relationship to adoptee. The reason for this replacement was to increase the number of biologic mothers for whom information was available by substituting group means for missing observations on their spouses. Regression analyses were conducted with each of the two sets of data.

To optimize the possibility of detecting nongenetic effects, we included all available adoptive families even when information on one or both biologic parents was missing. For example, in steps 1 and 2 of the analysis of sample A, there were 301 families for which there were no missing data on adoptive parents or the other two environmental variables but only 209 for which

there was full information about the biologic mothers. All steps in the analysis of sample B included information on 357 adoptive and biologic families.

#### **RESULTS**

As seen in table 2, the body mass index of biologic mothers was highly correlated with that of their daughters. There was a trend for the body mass index of biologic fathers to correlate with that of their daughters (p<.16). The failure to reach statistical significance may be due in part to the small number of observations (N=62) and in part to errors in estimates of paternal weights, most of which were reported by the biologic mothers. The correlations between the body mass index of biologic parents and their sons were positive, but the correlation with neither parent was statistically significant.

The correlations between adoptive parents and adoptees were low and nonsignificant. There was a significant correlation between the body mass indexes of the adoptive parents, while the correlation between the indexes of the biologic parents did not differ from

The correlations between biologic parents and adoptive parents, which provide a measure of selective placement, were small. Only one of the eight possible correlations—that of adoptive mothers with biologic fathers of female adoptees—was statistically significant (p=.04). In a larger sample in which the body mass indexes of adoptive and biologic parents (but not of adoptees) were available, none of the eight correlations (-0.07 to 0.18) was significant. The correlation of adoptive mothers with biologic fathers of female adoptées was only 0.18 (N=77, p=.12) in this larger sample.

Results of the regression analyses are presented in table 3. Note that the sample for which information on biological fathers was excluded (sample A) and the full sample (sample B) gave virtually identical results.

<sup>&</sup>lt;sup>b</sup>Pearson correlation, with age regressed out.

 $<sup>^{</sup>c}p<.001.$ 

p<.05.

<sup>&</sup>lt;sup>e</sup>p<.01.

TABLE 3. Hierarchical Regression Model for Residual Body Mass Index<sup>a</sup> in Study of Adoptees and Their Biologic and Adoptive Parents

(tem	Sample A: Data on Biologic Fathers Excluded <sup>b</sup>	Sample B: Data on Biologic Fathers Included <sup>c</sup>
Step 1: main effects, environmental	o ocad	0.045d
$\mathbb{R}^2$	$0.052^{d}$	0.045 <sup>d</sup>
Regression coefficients (±SE)	0.01 : 06	0.03   05
Adoptive mother (AM)	0.01±.06	$0.03 \pm .05$
Adoptive father (AF)	$-0.03 \pm .07$	$-0.02 \pm .07$
Rural/urban environment (RU)	$1.43 \pm .45^{d}$	$1.39 \pm .41^{d}$
Disturbance in home (D)	$0.99 \pm .42^{e}$	$0.75 \pm .38^{t}$
Step 2: interactions, environmental		
$\hat{R}^2$ (AM×AF, AM×RU, AM×D, AF×RU, AF×D, RU×D)	0.009	0.006
Step 3: main effects, genetic	,	3
$\mathbb{R}^2$	0.076 <sup>d</sup>	$0.061^{d}$
Regression coefficients (±SE)	,	11.
Biologic mother (BM)	$0.31 \pm .07^{\mathrm{g,h}}$	$0.31 \pm .07^{d,h}$
Biologic father (BF)		$0.17 \pm .13$
Step 4: interactions, Genetic by Environmental		
$\hat{R}^2$ (BM×AM, BM×AF, BM×RU, BM×D, BF×AM, BF×AF, BF×RU, BF×D)	0.039	0.025
Full model		
$\mathbb{R}^2$	0.176	0.137

<sup>&</sup>lt;sup>a</sup>Body mass index=weight in kilograms divided by the square of the height in meters.

Step 1, which included environmental variables, contributed significantly to adoptee body mass index. Both rural upbringing and a disturbed adoptive home environment predicted higher adoptee body mass indexes. The effect of disturbed home in sample B was only marginally significant. Notably, there was no significant relationship between the body mass index of either adoptive parent and that of the adoptee. Step 2, which included interactions of environmental variables, was not significant ( $r^2 < .01$ ).

Step 3, which assessed genetic effects, contributed significantly to adoptee body mass index, even after we controlled for all the other environmental variables and interactions in the model. The effect of biologic mother was highly significant, while that of biologic father was positive but nonsignificant (p=.19).

Step 4, which included interactions of genetic and environmental variables, was not significant (R<sup>2</sup>= 0.04). Of eight possible gene-environment interactions that were tested in this step, only one—that of adoptive father by biologic mother—was significant. The fact that this interaction was significant only in sample A and only at a 5% alpha level raises questions about its reliability, and we have not attempted an interpretation. Table 3 lists the interactions that were tested.

These data were originally collected to examine genetic and environmental influences on adoptee psychopathology. Therefore, it was of interest to determine the correlation between adoptee body mass index and specific psychopathology such as alcohol abuse and depression in the adoptee, and psychopathology such as alcohol problems and antisocial behavior in the biologic parents. No statistically significant correlations were found.

# DISCUSSION

The correlation in fatness, as defined by body mass index, of adoptees and biologic parents from whom they were separated at birth, indicates an influence of genetic factors on body weight that is independent of stature. The extent of influence also appears to be independent of adoptive parent body mass index and the other environmental factors that entered the predictive equations before genetic factors. The correlation between biologic parents and offspring applies to the full range of body fatness and is not restricted to the extremely obese or lean.

The best predictive model was an additive one in which genetic factors and nonfamilial environmental factors sum to determine fatness levels. Much of the variance in the regression model was unexplained. This variance may be due to nonfamilial environmental factors, aspects of the family environment that we were unable to assess, and genetic segregation. It is important to note that the maximum correlation between parents and children under complete genetic determination is only 0.5. Thus, the variance explained by biologic relationship is of practical as well as

<sup>&</sup>lt;sup>b</sup>For steps 1 and 2, 301 families included; for steps 3 and 4, 209 families included.

<sup>&</sup>lt;sup>c</sup>Means substituted for missing values; all 357 families included.

<sup>&</sup>lt;sup>d</sup>p<.01.

 $_{\rm p}^{\rm ep}$ <.05.  $_{\rm p}^{\rm f}$ =.05.

<sup>&</sup>lt;sup>g</sup>p<.001.

hWhile these two regression coefficients are based on somewhat different samples, they by chance round to the same values. The actual values are .3071±.0742 and .3147±.0695 for samples A and B, respectively.

statistical significance. The regression model was not used in the usual sense to obtain the best predictive model for adoptee body mass index or to estimate "heritability," the proportion of variance explained by genetic factors. For one thing, some environmental effects on fatness, e.g., those shared by siblings, which are known to be important during childhood (15), were not available in our study. Instead, we were interested in determining whether there was any evidence for genetic determination of fatness once environmental factors were controlled. We chose this approach because it makes no assumptions about mode of genetic or environmental transmission—assumptions that would be necessary in estimating heritability.

Selective placement—matching characteristics of adoptees and their biologic parents to those of adoptive parents—can potentially influence the characteristics of adult adoptees, either through direct matching or through similarity in rearing environments. This influence can thereby induce spurious correlations between adoptees and biologic parents. It is therefore worthy of note that no evidence of selective placement has been found in earlier studies of this population and only weak and equivocal evidence was found in this one. Selective placement on factors affecting fatness should result in a positive correlation between the body mass indexes of biologic and adoptive parents. In our study all eight observed correlations were low and only one was marginally significant (see table 2). In a larger sample from the Iowa adoption study, even this correlation did not differ from zero. Furthermore, no effect of adoptive parent body mass index on adoptee fatness was noted (see table 3). Finally, controlling for a possible correlation of genetic and environmental factors (including selective placement) by entering environmental variables first had no effect on the relationship of adoptee to biologic parents. Thus, it seems unlikely that selective placement accounted for the observed results.

This study identified two environmental factors that are related to adoptee body mass index: rural versus urban upbringing and disturbed rearing home environment. Rural populations tend to be slightly heavier than urban ones, according to current U.S. population data (28). However, the finding that disturbed family environment was associated with higher body mass index appears to be new and should be replicated. No single measure of disturbance in the family environment accounted for this effect. So, if the effect is real, it may be due to the general influence of stress.

The correlations in table 2 between biologic parents' body mass indexes and those of their offspring are somewhat stronger for daughters than for sons. Furthermore, the correlation between biologic mothers and their biologic offspring is stronger than the correlation of fathers with their offspring. Similar relationships among biologic parents and their offspring were found in Brazil (29) and in Denmark (16). The body mass index distribution of biologic mothers showed

greater positive skewness than did that of the other relatives. Reducing skewness by a log transformation of the body mass indexes, however, made only minor changes in the correlations of biologic mothers and daughters and did not affect the statistical significance of the various analyses. The higher correlation between biologic mothers and their offspring may be due in part to a gestational effect that increased the correlation of biologic mothers and their offspring and/or an error in the mother's reports of the biologic father's weight and height. These explanations, however, cannot account for the higher correlation of mothers with their daughters than with their sons. A similar pattern of correlations was found by Stunkard et al. (16) among Danish adoptees.

The youth of the biologic mothers and adoptees in our sample undoubtedly restricted their range of fatness relative to what it would have been at mid-life. Without this restriction the strength of the relationship of biologic parents to adoptees might have been stronger. An indication that bias resulting from this restriction is small is that studies of intact families have found parent-child correlations that are similar to those reported here (1, 2, 15, 28).

All traits require the coaction of genes and environment for their expression. Moreover, it is commonly believed that the expression of a complex trait like fatness requires interactions between genetic predisposition and environmental exposures. We attempted to assess this common-sense notion of interaction quantitatively by evaluation of specific statistical interactions between genetic background (indexed by biologic parents' body mass indexes) and environmental exposure (indexed by characteristics of the rearing parents, home, and community). Even though we found clear evidence of the effects of environment in the form of rural-urban differences and differences due to disturbance in the home, we did not find statistical evidence for any of the gene-environment interactions tested. We cannot, of course, rule out the existence of other, untested, environmental factors that may interact with genetic background. Major tasks of further research will be the identification of specific predisposing genetic and environmental factors, including their possible interactions.

#### REFERENCES

- Garn SM: Continuities and changes in fatness from infancy through adulthood. Curr Probl Pediat 1985; 15:1-47
- Mueller WH: The genetics of human fatness. Yearbook of Physical Anthropology 1983; 26:215-230
- Laskarzewski PM, Khoury P, Morrison JA, et al: Familial obesity and leanness. Int J Obes 1982; 7:505-527
- Brook CGD, Huntley RMC, Slack J: Influence of heredity and environment in determination of skinfold thickness in children. Br Med J 1975; 2:719-721
- Borjeson M: The aetiology of obesity in children. Acta Paediatr Scand 1976; 65:279–287
- Medlund P, Cederlof R, Flordus-Myrrhed B, et al: A New Swedish Twin Registry. Acta Med Scand (Suppl) 1976; 600
- 7. Feinleib M, Garrison RJ, Fabsitz R, et al: The NHLBI twin study of cardiovascular disease risk factors: methodology and

- summary of results. Am J Epidemiol 1977; 106:284-295
- 8. Fabsitz R, Feinleib M, Hrubec Z: Weight changes in adult twins. Acta Genet Med Gemellol 1980; 29:273-279
- Stunkard AJ, Foch TT, Hrubec Z: A twin study of human obesity. JAMA 1986; 256:51-54
- Withers RFJ: Problems in the genetics of human obesity. Eugen Rev 1964; 56:81–90
- Biron P, Mongeau JG, Bertrand D: Familial resemblance of body weight and weight/height in 374 homes with adopted children. Pediatrics 1977; 91:555–558
- 12. Annest JL, Sing CF, Biron P, et al: Family aggregation of blood pressure and weight in adoptive families, III: analysis of the role of shared genes and shared household environment in explaining family resemblances for height, weight and selected height/weight indices. Am J Epidemiol 1983; 117:492-506
- Garn SM, Bailey SM, Cole PE: Similarities between parents and their adopted children. Am J Phys Anthropol 1976; 45:539– 544
- Hartz A, Giefer E, Rim AA: Relative importance of the effect of family environment and heredity on obesity. Ann Hum Genet 1977; 41:185–193
- 15. Price RA: Genetics of human obesity. Annals of Behavioral Medicine 1987; 9:9-14
- Stunkard AJ, Sórenson TIA, Hanis C, et al: An adoption study of human obesity. New Engl J Med 1986; 314:193–198
- Cadoret RJ, Gath A: Inheritance of alcoholism in adoptees. Br J Psychiatry 1978; 132:252–258
- Cadoret RJ, Cain C, Grove W: Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. Arch Gen Psychiatry 1980; 37:561-563
- Cadoret RJ, O'Gorman T, Troughton E, et al: Alcoholism and antisocial personality: interrelationships, genetic and environ-

- mental factors. Arch Gen Psychiatry 1978; 55:176-184
- Cadoret RJ: Psychopathology in adopted-away offspring of biologic parents with antisocial behavior. Arch Gen Psychiatry 1978; 55:176–184
- Stunkard AJ, Albaum J: The accuracy of self-reported weights. Am J Clin Nutr 1981; 34:1593–1599
- 22. Wing RR, Epstein LH, Ossip DJ, et al: Reliability and validity of self-report and observer's estimates of relative weight. Addict Behav 1979; 4:133–140
- 23. Charney E, Goodman HC, McBride M, et al: Childhood antecedents of adult obesity: do chubby infants become obese adults? N Engl J Med 1976; 295:6-9
- 24. Coates TJ, Jeffery RW, Wing RR: The relationship between person's relatives' body weights and the quality and quantity of food stored in their homes. Addict Behav 1978; 3:179–184
- 25. Schlichting P, Hoilund-Carlsen PF, Quaade F: Comparison of self-reported height and weight with controlled height and weight in women and men. Int J Obes 1981; 5:67–71
- Palta M, Prineas RJ, Berman R, et al: Comparison of selfreported and measured height and weight. Am J Epidemiol 1982; 115:223–230
- 27. Benn RT: Some mathematical properties of weight-for-height indices used as measures of adiposity. Br J Prev Soc Med 1971; 25:42-50
- 28. Height and Weight of Adults Ages 18–74 by Socioeconomic and Geographical Variables in the United States: DHHS Publication PHS 81-1674. Hyattsville, Md, US Department of Health and Human Services, National Center for Health Statistics, August 1981, pp 17–18, 23, 38, 39
- Rao DC, MacLean CJ, Morton NE, et al: Analysis of family resemblance, V: height and weight in northeastern Brazil. Am J Hum Genet 1975; 27:509–520

# Some Physiologic Antecedents of Adult Mental Health

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The authors report on 188 healthy college men followed biennially from age 19 years to age 63. A relatively low standing heart rate and long treadmill running time in college predicted mental—but not physical—health during the next 40 years, whereas a relatively low blood pressure predicted future physical—but not mental—health. These relationships remained significant when the effects of physical fitness and body build were partialled out, suggesting that psychological components of physiologic phenomena accounted for their prediction of mental health outcome. The authors speculate that a high resting heart rate reflected social anxiety and prolonged running time reflected perseverance and stoicism.

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Attentive, my hand laid on the woman's wrist, I observed her pulse was irregular, suddenly violently agitated, which points to a troubled mind.

—Galen, cited by Mesulam and Perry (1)

In 1940, at the Harvard Fatigue Laboratory (an exercise physiology laboratory), 130 healthy college men participating in a study of normal young men (2) ran to near exhaustion on a treadmill and were carefully studied at rest. They had previously received a thorough physical examination. Because these men have been prospectively followed to age 63, they provide an opportunity to identify physiologic predictors of the mental and physical health of men over 40 years old.

Interest in heart rate as an index of psychological health dates back to at least the second century A.D., when Galen took a patient's pulse to diagnose emotional distress (1). The present study's original investigators noted that psychologically healthier college men tended to have slower heart rates (3). Since then, contemporary psychophysiologists have studied the

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significance of heart rate, largely in the laboratory, with a focus on short-term phasic changes induced by such stimuli as snake exposure (4), public speaking (5), and threat of shock (6). Large increases in heart rate are postulated not only to reflect psychological state but also to contribute to the development of cardio-vascular disease (7). In a rare nonlaboratory study, Shaffer et al. (8) found that young adults with higher resting heart rates were more likely to develop subsequent mental illness and hypertension. Paffenbarger et al. also linked high resting heart rate in young adults with later hypertension (9) and coronary heart disease (10). However, the relationship of heart rate to mental and physical health is far from established, and the mediating factors remain unclear.

Blood pressure also interested our study's originators. They believed that, like heart rate, it reflected the emotions and might prove useful as a personality index. Since the start of our study, studies have linked high adolescent blood pressure with future hypertension (11), coronary heart disease (12), and stroke (13). Whether emotions, behavior, and personality traits play a role in this relationship has been widely studied (14) but, again, mainly in the laboratory and without conclusive results.

Finally, our study's originators speculated that a long treadmill running time measured willpower and perseverance. Such psychological factors are indeed thought to be among the determinants of aerobic performance (15). However, no study that we know of has assessed the relationship of physical endurance and related psychological factors to subsequent psychological or physical health.

In this paper we examine the relationship of heart rate, blood pressure, and running duration in college to later mental and physical health. We do so from a longitudinal perspective, with a sample and with study conditions that allowed many potentially confounding variables to be controlled.

# METHOD

In 1940–1942 a university health service undertook an interdisciplinary study of 204 men from three sophomore classes (2). The health service and college deans had selected men who were without known academic, psychiatric, or physical health problems.

Physiologic studies were conducted in the Harvard

Fatigue Laboratory (16). After various measurements were made in the basal state, the subjects did two grades of work on a motor-driven treadmill (1). The first consisted of a 15-minute walk at 3.5 mph on an 8.6% grade. After 7 to 10 minutes of rest following the walk, the men did maximal work by running on the treadmill on the same grade at 7.0 mph until exhausted or for a maximum of 5 minutes. Oxygen consumption was measured during both grades of work; maximal oxygen consumption was attained after 2 to 3 minutes of running.

All sophomore subjects received a thorough physical examination performed by the same physician (2). Complete anthropometric assessments were also done, including somatotype and a rating of body build along a masculine-feminine continuum (2). The men were also studied by psychologists and psychiatrists. A family worker interviewed each subject at college and his parents at their home.

For 40 years, the surviving men have been followed prospectively by biennial questionnaires and twice by interviews (at age 30 and at age 47 or ages 55–60). The present data, except where noted, are derived from the questionnaires and have been shown to be reliable.

By 1964, six men had withdrawn from the study, five had died in World War II combat, and five had died of other causes. This left 188 men for the study of mental health at midlife (17). Since then an additional 19 men have died, further reducing the sample size for later data analyses.

# Antecedent Measures

College run duration (N=130). This was the duration of the fatigue laboratory treadmill run; the maximum was 300 seconds.

College physical fitness (N=66). The best objective measure of physical fitness is maximal oxygen consumption during exercise divided by body weight to adjust for differences in muscle mass (ml/kg per minute). Maximal oxygen consumption was measured during the treadmill run.

College standing heart rate (N=188). Heart rate (pulse) was obtained during the physical examination with the subject in a standing position as well as in a sitting and a recumbent position.

College diastolic blood pressure (N=198). Blood pressure was measured during the physical examination with the subject in a recumbent position.

College body build (N=188). With the aid of a standardized chart, subjects' body builds, photographed from the front, side, and rear, were classified on a 4-point scale on which 1=a strong, 2=a moderate, 3=a weak, and 4=a very weak masculine component.

Childhood (ages 0–18 years) environment (N=188). Each man's childhood was rated on a scale of 1 (bleak) to 20 (warm) by two research associates who were blind to all data gathered after the man was 19 years old. The scale is described in detail elsewhere (18) and

was based on interviews with the parents and on psychiatric interviews with the sophomore men. (Rater reliability was .71.)

#### Outcome Measures

Except for estimates of psychological adjustment at age 29, these ratings were made by raters blind to previous ratings.

Psychological adjustment, ages 22–29 (N=111). Using all data from the previous 10 years, the staff reviewed each subject's history and assigned by consensus prognostic ratings for future personality stability. A rating of 1 indicated best stability, and 5 indicated worst stability.

Psychological adjustment, ages 30–47 (N=188). An adult adjustment scale, described in detail elsewhere (17, 19), was derived from earlier empirical work on the global mental health of each subject. The scale's range from 7 (best) to 16 (worst) was derived from the cumulative ratings of seven relatively objectively and longitudinally observed items. Five variables were scored 2 (true) or 1 (untrue): 1) little occupational advancement, 2) limited recreation with others, 3) less than 2 weeks' annual vacation, 4) more than 5 days' annual sick leave, and 5) earned annual income less than \$20,000 (1968 dollars). Two variables were scored 3 (definite), 2 (ambiguous), or 1 (untrue): 1) marriage rated by self and wife as unhappy and 2) chronic job dissatisfaction.

Psychological adjustment, ages 48–63 (N=174). This scale was similar to that used for subjects at ages 30–47 except that the income item was replaced by retirement before age 65 (absence=1, partial=2, presence=3). Three items were added: 1) psychiatric visits since age 48 (2 points), 2) tranquilizer use since age 48 (2 points), and 3) a rater's estimate of "global adaptation to aging" (5 points).

Psychiatric visits (N=174). Number of visits to a psychiatrist from age 20 to age 63.

Sick days (N=177). Mean number of days of sick leave per year from age 20 to age 60.

Marital stability (N=181). Overall quality of marriage from age 20 to age 60 was assessed on the basis of questionnaire data gathered from the husband and wife on five occasions. A marriage rated 1 was relatively happy and of at least 25 years' duration; a marriage rated 4 ended in divorce without satisfactory remarriage.

Mood-altering drug use (N=188). Use of sleeping pills, tranquilizers, or amphetamines from age 30 to age 52 was assessed on a scale of 1–5: 1=no drug use and 5=hospitalization or socioeconomic damage due to drug use.

Physical health (N=188). Records of complete physical examinations were obtained in 1969, 1974, 1979, and 1984. These were rated by an internist kept blind to other study data. Almost 85% of the examinations included routine laboratory studies, ECG, and chest X-rays. The ratings were 1=excellent health (no

TABLE 1. Correlations<sup>a</sup> Between Adult Health and Childhood Environment and College Heart Rate, Run Duration, and Diastolic Blood Pressure

Adult Health	Childhood	College	College Run	College Diastolic
	Environment <sup>b</sup>	Heart Rate	Duration	Blood Pressure
	(N=188) <sup>c</sup>	(N=184) <sup>c</sup>	(N=127) <sup>c</sup>	(N=188) <sup>c</sup>
Psychological health Psychological adjustment Ages 20–29 years Ages 30–47 years Ages 48–63 years Psychiatric visits, ages 20–60 years Days sick, ages 20–60 years Marital stability, ages 20–60 years Mood-altering drug use, ages 20–60 years	44 <sup>d</sup> 31 <sup>d</sup> 24 <sup>e</sup> 23 <sup>e</sup> 17 <sup>f</sup> 13 <sup>f</sup> 11	.21° .27d .28d .14f .14f .10	22° 16 <sup>f</sup> 14 29° 22° 18 <sup>f</sup> 14	.13 <sup>f</sup> .01 .10 .01 .00 23 <sup>e</sup> 03
Physical health Age 40 years Age 50 years Age 60 years	04	.03	08	.12
	15 <sup>f</sup>	.12	15 <sup>f</sup>	.16 <sup>f</sup>
	20 <sup>e</sup>	.09	11	.16 <sup>f</sup>

<sup>&</sup>lt;sup>a</sup>Spearman rank-order correlation coefficients were used for calculations in which at least one variable had fewer than nine values; Pearson product-moment correlation coefficients were used for all others. Since low values for all health variables indicated health, the positive associations of mental and physical health with warm childhood and long running times are expressed as negative correlations.

irreversible pathology), 2=minor chronic problems, 3=irreversible serious illness without disability, 4=irreversible illness with disability, and 5=dead.

## **RESULTS**

Table 1 shows that a relatively low college heart rate and long college running time predicted future mental—but not physical—health, whereas a relatively low college blood pressure predicted future physical—but not mental—health.

College heart rate (mean±SD=82±14 beats/minute, range=54–120 beats/minute) predicted mental health outcome nearly as well as did childhood environment, the study's most robust predictor variable. A high heart rate was associated with poor psychological adjustment from age 22 to age 63 and with several psychological components: psychiatric visits, sick days (a measure in this sample of mental rather than physical illness [3]), and use of tranquilizers, sleeping pills, and amphetamines.

A relatively long college running time (mean=239±67 seconds, range=93-300 seconds) also predicted future mental health. Unlike heart rate, running time did not predict psychological adjustment at midlife or mood-altering drug use, but it did predict stable marital commitment.

College diastolic blood pressure (mean=71±9 mm Hg, range=40–95 mm Hg) had a different correlation pattern: high diastolic pressure predicted deterioration of physical health but did not predict mental health outcome except for—surprisingly—a stable marriage. Run duration, heart rate, and childhood environment significantly intercorrelated with one another, whereas

blood pressure correlated with none of these other antecedent variables.

To determine whether the *psychological* component of run duration and heart rate accounted for their predictive power, we computed partial correlations to control the potentially mediating variables of physical fitness and body build for run duration and physical fitness for heart rate. When physical fitness and body build (for the 60 subjects with available data) were controlled for in this way, eight of the 12 significant correlations in table 1 remained significant, including psychological adjustment at all ages with heart rate and at ages 30-47 with college run duration (despite a decrease of statistical power to .38 because of the reduced sample size). This suggests that it was the psychological component of run duration and heart rate that accounted for their prediction of mental health outcome.

#### **DISCUSSION**

Our finding that men with a higher standing heart rate at age 19 were not as psychologically "sound" in college (r=.25, N=184, p<.001) or during the next 40 years concurs with the observation of Shaffer et al. (8) in the only other longitudinal study that has assessed the predictive value of heart rate for later mental health. The correlations in table 1 of .11 to .39 should not be viewed as trivial. An exhaustive review of correlations between personality variables observed across 20 years or more (20) revealed that correlations of .3 are as high as are commonly observed.

Factors influencing heart rate in healthy people are age, sex, sleep, body position, muscular activity, phys-

bHigh score=warm; low score=bleak.

Number varies by 10% on some correlations due to attrition by death as men grew older.

<sup>&</sup>lt;sup>d</sup>p<.001.

<sup>&</sup>lt;sup>e</sup>p<.01.

 $<sup>^{</sup>f_{p}^{2}}$ <.05.

ical fitness, and emotional arousal (21). The first five factors were held constant by virtue of our study design and homogeneous sample. When the sixth factor, physical fitness, was controlled for, most correlations of heart rate with outcome variables remained significant. Thus, in this study, emotional arousal—the remaining factor—may account for the association of heart rate with mental health outcome.

Although heart rate can increase in response to many different stimuli and emotional states (22), we speculate that in the setting of a physical examination, which required close interaction and physical contact with another person, emotional arousal reflected social anxiety. Socially anxious adults have a larger increase in heart rate during social interactions than those who are not socially anxious (23), and socially inhibited children have a higher resting heart rate than socially uninhibited children (24).

Astrand and Rodahl (15) described five factors that influence the ability to perform sustained physical work such as treadmill running: 1) nature of the work (e.g., intensity and technique), 2) environment (e.g., altitude and ambient temperature), 3) somatic factors (e.g., sex and body build), 4) physical fitness, and 5) psychological factors (motivation and attitude). In our study, sex, nature of the work, and environment were held constant by the study design and laboratory conditions. Partialling out physical fitness and body build had little effect on the correlation of running time with the mental health outcome variables. Thus, again, psychological factors—the only remaining variable seems the most logical explanatory variable. Indeed, Astrand and Rodahl stated that "physical performance is to a significant extent a function of psychological factors, notably motivation, attitude to work, and the will to mobilize one's resources for the accomplishment of the task in question" (p. 451). For patients with chronic bronchitis, positive attitudes were more important than pulmonary function tests in predicting aerobic exercise tolerance (15). However, we do not conclude that physical fitness is irrelevant to physical and mental health. Rather, we conclude that in this sample, selected without reference to athletic ability or physical fitness, psychological factors were the important factor.

Astrand and Rodahl's "motivation," "attitude," and "will" require more precise definition. We speculate that such terms may reflect suppression, the ego mechanism of defense most powerfully correlated with multiple facets of mental health in previous studies of these men (25) and inner-city men (19, 25). In these studies, suppression was defined as the conscious or semiconscious decision to postpone paying attention to a conscious impulse or conflict, minimizing but not denying discomfort and anxiety, looking for silver linings, and employing a stiff upper lip—in short, being stoical and persevering (26). The study of adult development by Terman and Oden (27) also suggested that suppression in adolescence was important to mental health and vocational success at age 50. We suspect

but cannot prove that perseverance, stoicism, and suppression reflect facets of a common trait. In our study, the use of suppression from age 20 to age 47 (assessed on a 4-point scale) correlated at .22 (N=127, p<.01) with duration of the treadmill run. It also correlated at -.25 (N=183, p<.001) with college heart rate. Although some studies have linked suppression of anger and hostility with higher blood pressure, others have not (14, 28); we found that suppression did not correlate with diastolic blood pressure (r=.06, N=187).

Because so many disparate influences and discontinuities exist in the life span, it is notable that two physiologic variables—heart rate and running duration—studied in late adolescence should have predicted future mental health nearly as well as did childhood environment, the most robust predictor. As Baldwin (29) has written, "Longitudinal studies seem to have gambled on the existence of clear developmental trends that would shine through the welter of influences of uncontrolled events." It is gratifying to find that such trends do exist.

#### REFERENCES

- Mesulam M, Perry J: The diagnosis of love-sickness: experimental psychophysiology without the polygraph. Psychophysiology 1972; 9:546-551
- 2. Heath CW: What People Are: A Study of Normal Young Men. Cambridge, Harvard University Press, 1945
- Hooton E: Young Man, You Are Normal. New York, GP Putnam's Sons, 1945
- Lang PJ, Levin DN, Miller, GA, et al: Fear behavior, fear imagery, and the psychophysiology of emotion: the problem of affective response integration. J Abnorm Psychol 1983; 92: 276-306
- 5. Knight ML, Borden RJ: Autonomic and affective reactions of high and low socially-anxious individuals awaiting public performances. Psychophysiology 1979; 16:209–213
- Hodges WF, Spielberger CD: The effects of threat of shock on heart rate for subjects who differ in manifest anxiety and fear of shock. Psychophysiology 1966; 2:287–294
- Lovallo WR, Picomb GA, Wilson MF: Heart rate reactivity and Type A behavior as modifiers of physiological response to active and passive coping. Psychophysiology 1986; 23:105-112
- Shaffer JW, Duszynski KR, Thomas CB: A multivariate analysis
  of circulatory data and their relationship to later disease. J
  Chronic Dis 1983; 36:869–877
- Paffenbarger RS, Thorne MC, Wing AL: Chronic disease in former college students, VIII: characteristics in youth predisposing to hypertension in later years. Am J Epidemiol 1968; 88:25— 32
- Gillum RF, Paffenbarger RS: Chronic disease in former college students, XVII: sociocultural mobility as a precursor of coronary heart disease and hypertension. Am J Epidemiol 1978; 108:289-298
- Oberman A, Lane NE, Harlan WR, et al: Trends in systolic blood pressure in a 1000 aviator cohort over a 24 year period. Circulation 1967; 36:812–822
- Thorne MC, Wing AL, Paffenbargér RS: Chronic disease in former college students, VII: early precursors of nonfatal coronary heart disease. Am J Epidemiol 1968; 87:520-529
- 13. Kannel WB, Wolf PA, Verter J, et al: Epidemiologic assessment of the role of blood pressure in stroke: the Framingham Study. JAMA 1970; 214:301-310
  14. Waal-Manning HJ, Knight RJ, Spears GF, et al: The relation-
- ship between blood pressure and personality in a large unselected adult sample. J Psychosom Res 1986; 30:316–368

- 15. Astrand P, Rodahl K: Textbook of Work Physiology: Physiological Bases of Exercise. New York, McGraw-Hill, 1977
- Horvath SM, Horvath EC: Harvard Fatigue Laboratory: Its History and Contributions. Englewood Cliffs, NJ, Prentice-Hall, 1973
- Vaillant GE: Natural history of male psychological health, VII: effects of mental health on physical health. N Eng J Med 1979; 67:1249–1254
- Vaillant GE: Natural history of male psychological health, II: some antecedents of healthy adult adjustment. Arch Gen Psychiatry 1974; 31:15–22
- 19. Vaillant GE: Adaptation to Life. Boston, Little, Brown, 1977
- Kohlberg L, LaCrosse J, Ricks D: The predictability of adult mental health from childhood behavior, in Manual of Child Psychopathology. Edited by Wohlman BB. New York, McGraw-Hill, 1972
- Berne RM, Levy MN (eds): Physiology. St Louis, CV Mosby, 1983
- 22. Schwartz GS, Weinberger DA, Singer JA: Cardiovascular differentiation of happiness, anger, and fear following imagery and

- exercise. Psychosom Med 1981; 43:343-364
- Beidel DC, Turner SM, Dancu CV: Physiological, cognitive, and behavioral aspects of social anxiety. Behav Res Ther 1985; 23: 109–117
- Kagan J, Reznick JS, Clarke C, et al: Effect of attitudes and beliefs on exercise tolerance in chronic bronchitis. Br Med J 1983; 286:171–173
- 25. Vaillant GE, Drake RE: Maturity of ego defenses in relation to personality disorders. Arch Gen Psychiatry 1985; 54:597–601
  26. Vaillant GE: Theoretical hierarchy of adaptive ego mechanisms.
- Vaillant GE: Theoretical hierarchy of adaptive ego mechanisms Arch Gen Psychiatry 1971; 24:107–118
- 27. Terman LM, Oden MH: The Gifted Group at Mid-Life. Stanford, Calif., Stanford University Press, 1959
- 28. Julius M, Harburg E, Cottington E, et al: Anger-coping types, blood pressure, and all-cause mortality: a follow-up in Tecumseh, Michigan (1971–1983). Am J Epidemiol 1986: 124:220–223
- Baldwin AL: The study of child behavior and development, in Handbook of Research Methods in Child Development. Edited by Mussen PH. New York, John Wiley & Sons, 1960

#### Change of Address for American Board of Psychiatry and Neurology

As of June 15, 1987, the address and telephone number of the American Board of Psychiatry and Neurology were changed to the following:

American Board of Psychiatry and Neurology, Inc. 500 Lake Cook Rd., Suite 335 Deerfield, IL 60015 (312) 945-7900

# A Naturalistic Study of Imipramine in Panic Disorder and Agoraphobia

Thomas A. Aronson, M.D.

This naturalistic study examined the treatment response to imipramine of 60 patients who had panic disorder or agoraphobia with panic attacks. Only half of the patients could tolerate the drug, but of those who did, 88% obtained a markedly beneficial clinical effect. An amphetamine-like side effect accounted for most of the dropouts. More than one-half of the responders achieved clinical remission at doses (≤100 mg/day) and plasma levels (≤150 ng/ml) considered to be subtherapeutic for depression. There appears to be neither a clear threshold for response nor a therapeutic dose range for imipramine in the treatment of panic. Doses should be adjusted individually and increased conservatively. (Am J Psychiatry 1987; 144:1014–1019)

Multiple controlled studies have demonstrated the efficacy of tricyclic antidepressants combined with supportive or behavioral therapy in the treatment of panic disorder and agoraphobia (1–4). However, studies differ markedly in terms of drug doses and treatment recommendations to clinicians, particularly in regard to imipramine, the drug about which the most reports have been made to date.

For example, Marks et al. (5) found that imipramine was no more effective than placebo and that neither the dose nor the plasma concentration of the drug correlated with improvement. On the other hand, Sheehan et al. (6) reported a significant treatment effect with imipramine, 150 mg/day, which, however, appeared to be less robust than the effect with phenelzine, 45 mg/day. Both of these studies have been criticized for using lower mean imipramine doses than were used in studies by Zitrin et al. (1, 2), who found significant imipramine effects. In addition, Mavissakalian et al. reported a positive association between dose (7) and plasma level (8) and improvement in agoraphobia. This improvement correlated significantly only with

plasma imipramine levels, not desipramine or combined levels; moreover, there was no correlation between plasma levels and improvement in panic attacks. These results were also contradicted; Ballenger et al. (9) found significant treatment effects in agoraphobia but no clear correlation between plasma levels and response. They suggested that patients whose plasma levels were maintained in the lower range (100–150 ng/ml) seemed to respond better clinically than those whose levels were in the higher range (200–250 ng/ml). More confusing, there have been several anecdotal reports (10–13) that very small doses of imipramine (10–25 mg/day) are sometimes clinically effective.

To summarize, most studies agree that imipramine works in the treatment of agoraphobia but disagree at what dose or plasma level. It remains controversial whether patients with panic disorder or agoraphobia should have doses or plasma levels similar to those of patients with depression.

Compared to the limited studies of imipramine in panic disorder and agoraphobia, the relationship between plasma level and clinical outcome in depression is clearest and most straightforward with imipramine. At least seven studies (14–20) measuring both imipramine and its desmethylated metabolite desipramine have consistently found a linear or sigmoidal relationship between the plasma desipramine level and/or the combined plasma level and clinical outcome.

Although most panic and agoraphobic patients have benefited from imipramine in controlled clinical trial settings, to my knowledge there have been no previous naturalistic studies of how patients fare in typical treatment settings: how many actually tolerate the medication, how many benefit, doses and plasma levels required to achieve clinical remission, dropout rates, frequency of problematic side effects, and reasons for treatment failure. This report describes the imipramine treatment of 60 patients with panic disorder and agoraphobia.

# **METHOD**

The study involved a cohort of 60 consecutive self-referred patients who met the *DSM-III* criteria for panic disorder or agoraphobia with panic attacks, as judged by two clinical raters. They were treated in a

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university hospital anxiety disorders clinic in an open, nonblind clinical trial of imipramine plus individual behavioral therapy.

Initially, we gave the patients doses of imipramine similar to the usual doses for treatment of a major depressive disorder, i.e., rapid titration to 150-200 mg/day. For reasons to be discussed later, we soon abandoned this strategy and began to use a conservative dose based on a dose-response strategy: in both diagnostic groups doses were started at 25 mg/day and increased by 25-50 mg/week up to 100 mg/day and thereafter by 50 mg/week up to 300 mg/day only if panic attacks continued to occur. For those patients with phobic and avoidant complications who reached an apparently stable dose, behavioral homework assignments were encouraged for testing the antipanic efficacy of the drug. We tried to treat patients with the lowest possible effective doses. The stable maintenance doses at which they remained panic free for at least 1 month are reported here. Panic free was defined as the absence of both spontaneous and situational panic attacks that met DSM-III criteria.

After 4 months of treatment, the patients' responses to treatment were globally rated by the treating physicians as excellent, good, fair, or poor. The patients with ratings of good or excellent were panic free but differed in the degree of improvement of their phobic avoidance. Patients with a rating of fair showed only limited improvement in panic or phobias, and those with a rating of poor did not improve. Because of the limited number of patients, the good and excellent and the fair and poor groups were combined for purposes of analysis. No systematic rating scales or behavioral measures were used, however.

Eighteen patients (30%) terminated prematurely, usually by the fourth therapy session. Reasons for premature termination were assessed at the time of the last appointment or by a subsequent telephone call, but they could not be determined for six patients. The other 42 patients (70%) remained in treatment for 4–12 months; 33 took imipramine and nine were switched to a secondary tricyclic antidepressant, phenelzine, or alprazolam. Although the outcomes of patients who were switched to other medications were very similar, for the purposes of this discussion I present data only for those who took imipramine the whole time.

Side effects were spontaneously reported by patients; a structured questionnaire about side effects was not used. We also noted how many patients complained of a stimulant response and tried to reassure these patients and/or lower the dose before switching to another medication.

Once a patient was panic free and had been taking a stable dose of imipramine for at least 1 month, blood was drawn 10–12 hours after ingestion of the drug for determining plasma levels. All patients were questioned carefully about compliance with their drug regimens, and all appeared to have cooperated fully, although compliance was not reliably validated. Imip-

ramine and desipramine plasma levels were determined by the gas chromatographic technique (at Smith Kleine Bioscience). Eighteen of the 29 patients who became panic free while taking imipramine agreed to having blood drawn for determining plasma levels.

#### **RESULTS**

Twenty-nine patients (48% of the original cohort of 60) had good to excellent outcomes with imipramine, and four had a fair or poor clinical response to it. Six patients dropped out for unknown reasons. Three others refused or were refused medication altogether: two were pregnant, a third schizotypal. Eighteen patients had intolerable side effects, and only nine of these continued in the clinic and achieved good to excellent outcomes with phenelzine, alprazolam, or a secondary tricyclic. In total, 18 patients (30%) prematurely terminated treatment, and 38 (63%) had good to excellent outcomes.

The major known reason for early dropouts was medication intolerance (nine patients). In all, 18 patients could not tolerate the imipramine because of side effects: 13 had a stimulant reaction, two had an anticholinergic reaction, one had an allergic reaction, and two had an orthostatic reaction. Excluding the nine who refused or prematurely dropped out, this represents 35% (18 of 51) of the total sample. Only half of these patients continued treatment with another drug. By far the greatest cause of medication intolerance was an initial amphetamine-like response (13 patients), which has been previously described in panic disorder. This involved complaints of increased generalized anxiety, insomnia, tremulousness, and tachycardia. Besides the nine patients who prematurely terminated and the four who switched to another medication because of the stimulant reaction, another six patients were able to tolerate the stimulant response until it disappeared, and they continued to take imipramine. Thus, 19 (37%) of the 51 patients experienced a stimulant reaction to the imipramine, which was tolerated and eventually disappeared (generally, in 3-14 days) in a third of them (six patients) but led to premature termination (after the first or second session) in half (nine patients).

Of the patients who could tolerate the imipramine, 88% (29 of 33) achieved good to excellent outcomes; that is, panic attacks disappeared, and although phobic behavior typically lagged behind in improvement, by 4 months notable gains had also been made. Table 1 presents the age, sex, diagnoses, doses, and plasma levels at which the 29 patients taking imipramine became panic free.

For the entire 29, the mean±SD dose of imipramine was 130±75.3 mg/day, and the range was 25–300 mg/day. For the 18 of the 29 whose plasma levels were also ascertained, mean±SD imipramine, desipramine, and combined levels were 61.8±57.1 ng/ml, 108±122.1 ng/ml, and 186±190 ng/ml, respectively. The

TABLE 1. Doses of Imipramine and Plasma Levels of Imipramine and Desipramine at Which 29 Patients With Panic Disorder or Agoraphobia With Panic Attacks Became Panic Free

				Imipramine		Plasma Level					
Patient	Age (years)	Sex	Axis I Diagnoses	Dose (mg/day)	Imipramine (ng/ml)	Desipramine (ng/ml)	Combined (ng/ml)				
1	38	F	Agoraphobia with panic attacks; alcohol abuse	25	0	0	0				
2	41	F	Agoraphobia with panic attacks	25	22	0	22				
3	35	F	Agoraphobia with panic attacks	50	25	37	62				
4	22	F	Agoraphobia with panic attacks	75	23	0	23				
5	36	F	Agoraphobia with panic attacks	75	30	114	144				
6	27	F	Agoraphobia with panic attacks	100	45	42	87				
7	35	F	Agoraphobia with panic attacks; diazepam dependence	100	28	28	56				
8	34	M	Panic disorder	100	26	30	56				
9	36	M	Panic disorder	100	51	61	112				
10	32	F	Panic disorder	150	84	179	263				
11	37	F	Panic disorder	150	63	61	124				
12	24	M	Panic disorder; simple phobias	150	19	38	57				
13	27	F	Agoraphobia with panic attacks; major depression	200	182	257	43				
14	42	F	Agoraphobia with panic attacks	200	110	312	422				
15	35	F	Agoraphobia with panic attacks	200	268	362	630				
16	38	F	Agoraphobia with panic attacks	200	54	183	237				
17	46	F	Agoraphobia with panic attacks	250	205	89	294				
18	44	F	Agoraphobia with panic attacks; major depression	300	83	420	508				
19	42	M	Panic disorder; dysthymic disorder	50		_	_				
20	26	F	Panic disorder	50		_					
21	25	F	Agoraphobia with panic attacks	75							
22	29	F	Panic disorder	75		_	_				
23	38	M	Panic disorder	100		_	_				
24	20	F	Panic disorder	100		_	_				
25	36	M	Panic disorder; psychogenic pain disorder	150		_					
26	36	F	Agoraphobia with panic attacks	150		_	_				
27	30	F	Agoraphobia with panic attacks	150		_					
28	45	F	Agoraphobia with panic attacks	200		_	_				
29	41	F	Panic disorder	300		_	_				

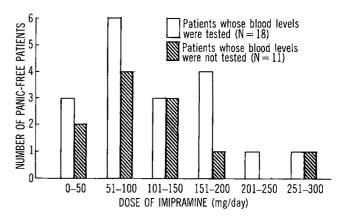
total levels ranged from 0 to 630 ng/ml. The large standard deviations and dose ranges suggest a wide variation in clinical responsiveness.

Two-tailed t tests showed no significant differences in dose (t=0.45, df=26, p=.66) between the patients with panic disorder (N=12; mean±SD dose=123±67 mg/day) and the patients with agoraphobia with panic attacks (N=17; 136±82 mg/day). There were also no significantly different dose requirements (t=0.80, df=26, p=.43) between the men (N=6; mean±SD dose=108±37 mg/day) and the women (N=23; 136±82 mg/day).

Four patients taking imipramine did not do well. Two of them had borderline personality disorders: one later overdosed on imipramine and alprazolam; another had her panic attacks subsequently controlled by phenelzine but could not generalize the positive clinical effect into other areas of her chaotic life. A third patient started to have attacks of suddenly falling asleep. Eventually, both narcolepsy and mitral valve prolapse were documented, and after several medication trials his symptoms were finally controlled with methylphenidate and propranolol. Another patient, who was chronically agoraphobic and had only situational, nonspontaneous panic attacks, could not be engaged in exposure therapy to test the effectiveness of the antipanic medication.

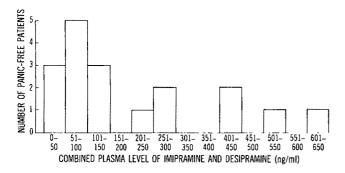
Figures 1 and 2 illustrate the doses and combined

FIGURE 1. Doses of Imipramine at Which Patients With Panic Disorder or Agoraphobia With Panic Attacks Stayed Panic Free



plasma levels at which patients were maintained panic free. One can observe from these figures that 1) 52% (15 of 29) achieved clinical remission at doses of 100 mg/day or less, which are usually considered subtherapeutic for depression; 2) 61% (11 of 18) of the responders had combined plasma levels below the usual therapeutic range for depression, reported in our laboratory as 150–300 ng/ml; 3) four patients had supranormal plasma levels (>300 ng/ml), two of whom were the only endogenously depressed patients

FIGURE 2. Combined Plasma Levels of Imipramine and Desipramine at Which Patients With Panic Disorder or Agoraphobia With Panic Attacks Stayed Panic Free



in the entire sample. It should also be mentioned that one of the two patients who responded at a dose of 25 mg/day had a plasma level of 0 ng/ml, which was probably due to laboratory artifact rather than non-compliance; she was upset when she was later told to stop the medication because she had become unexpectedly pregnant and was eager to restart after the pregnancy was terminated.

#### **DISCUSSION**

The results of this study should be regarded as tentative, as there were a number of methodological limitations in its naturalistic design. No objective symptom or behavioral rating scales were used, and no systematic observations were made concerning response. Instead, patients' responses were globally rated by the treating physicians. Since only 18 of the 29 patients who improved while taking imipramine agreed to have their plasma levels measured, the plasma level data may not be a representative sample. This was not a dose-response study. Plasma levels and maintenance doses are reported only for those who became panic free and had good to excellent outcomes after 4 months of treatment; hence, it is difficult to make any direct comparisons with the contradictory results of dose-response studies (7–9). The data do not allow any conclusions about whether the imipramine, desipramine, or combined plasma levels correlated with clinical improvement. Previous studies have reported either no correlation or correlation with plasma imipramine level only, unlike the correlations found in depressed patients.

However, our design allowed discrimination of response at lower doses, which was not possible in the previous studies. Presumably, if most of the patients in this study had been given higher doses, they would have responded at the same rate; they simply would have been given too much medicine. Our control over medication compliance and the timing of plasma level determination was limited. Even if medication compliance had been suspect, however, it would only have biased the results in favor of responsiveness to low

doses, which, as this article has emphasized, is quite common.

Only one-half of our patients (29 of 60) did well on imipramine; 18 others refused or dropped out prematurely. Another nine did well on other antipanic medications they switched to because of intolerable side effects. For those who could tolerate imipramine, the vast majority (88%, or 29 of 33) did exceptionally well; that is, they became panic free, although improvement in phobic avoidance typically lagged behind. It was our clinical impression that it generally took 3–6 weeks for patients to become panic free but 3–6 months for a considerable reduction of their phobic avoidance and anticipatory anxiety.

Intolerable side effects were quite common, particularly the amphetamine-like reaction, which we have observed only in patients with panic disorder. In our limited experience, it appears that this most common, problematic side effect typically occurs at the beginning of treatment, is dose related, recurs if one switches to another tricyclic amine or to phenelzine but not alprazolam, and requires much support and encouragement to keep the patient in treatment. Subsequent clinical experience suggests that the adjunctive use of alprazolam can reduce or eliminate this side effect, but this notion requires further study.

The few patients (four of 33) who did not improve with imipramine had axis I diagnoses other than panic disorder or agoraphobia, were borderline personalities, or simply could not be induced to try exposure to situations in which they had previously panicked. It was our clinical impression that many agoraphobic patients with primarily situational, provoked panic attacks were reluctant to test out the efficacy of their antipanic medication. There is disagreement about whether imipramine has an additional antiphobic effect that lags behind its antipanic effect. For example, Mavissakalian et al. (7–8) found a correlation between dose, plasma levels, and improvement in agoraphobia, not panic attacks. However, our experience with agoraphobic patients who responded partially or not at all to medication suggests that motivation to try exposure in vivo is the key element. In fact, we have since treated three severely agoraphobic women whom medications have made panic free but who have made quite limited gains in terms of their avoidance behavior. Consequently, we now emphasize to patients that the medications only block panic attacks and that it will be their responsibility, with our help, to overcome their phobic avoidance.

Our relatively high dropout rate (30%, N=18) actually compares well with those in other controlled studies: Marks et al. (5) had 36%, Sheehan et al. (6) had 26%, and Zitrin et al. (1) had 21%. It reflects in part the clinical inexperience of the psychiatric residents who staffed the anxiety disorders clinic, as well as an inherent feature of the naturalistic design of the study, since potential noncompleters were not screened out. However, it also raises the issue of how acceptable treatment of agoraphobia by medication is to a wider

group of patients. A review of a large number of studies indicated that the median dropout rate from exposure-based treatment for agoraphobia was 12% (21), but this figure rises to 25%—40% when drugs are added or when the exposure in vivo is intensive rather than graduated and self-paced (22). Studies are needed to further delineate why it is difficult to retain these patients in treatment, as well as to define strategies to lower the attrition rate. It was our clinical impression that these patients are often quite preoccupied with somatic problems and are hypochondriacal in their reactions to side effects.

The doses and plasma levels at which our patients became panic free and achieved good to excellent outcomes suggest several practical clinical points.

- 1. Slightly more than one-half of the patient sample responded to imipramine doses of 100 mg/day or less and at combined imipramine and desipramine plasma levels of 150 ng/ml or less, which are usually considered subtherapeutic for the treatment of depression. In fact, this may represent an underestimate of the lowdose responders, since, as previously mentioned, the first patients in the treatment program were given doses similar to those for depression, and medication compliance in this outpatient sample could not be ensured. Although we did not have enough data points to conclude whether there was a bimodal, continuous, or some other type of distribution of effective doses or blood levels, there was certainly a tremendous variation. Again, it cannot be assessed from our data whether this represented a duration effect (i.e., low doses given long enough produce the same response as high doses do) or different neurobiological subgroups; however, it does suggest that imipramine's antipanic effect may involve a different neurobiological mechanism from that of its antidepressant effect, given the different range of doses and plasma levels. From our data it appears that there may be no clear threshold for response and no well-defined therapeutic range but, rather, a continuous curve of responders. Clinically, in other words, a patient's dose must be individually titrated. Clinical response rather than reaching a presumably therapeutic blood level is what matters.
- 2. A few patients required quite high doses and plasma levels, and a few responded to quite low ones. Similar idiosyncratic responses to high doses and plasma levels have also been reported among patients with major depression (23). It is noteworthy that two of our four high-dose patients had coexistent severe endogenous depression. An unresolved question is whether the severity of depression affects the dose needed. Patients with major depression complicating their panic disorder or agoraphobia may need doses and plasma levels that would be appropriate for treating depression. We did not examine a related issue that is, the relationship between the severity of the panic disorder and the dose requirement. The relatively high prevalence of intolerance to imipramine in panic disorder and the responsiveness to low doses (53%) suggest that patients should be started slowly

and conservatively at low doses (10 or 25 mg/day) when they are being treated for panic disorder with or without agoraphobia.

3. My colleagues and I question the need for determining plasma levels of imipramine in panic disorder, except perhaps to monitor compliance, identify slow metabolizers, and avoid potentially toxic levels in geriatric and medically ill patients. Our data suggest that there may not be a threshold of response or a clear-cut therapeutic range, as there seems to be in depression. Even though these results contradict those of Mavissakalian et al. (7, 8), they are consistent with those of the controlled study by Ballenger et al. (9). The response in panic disorder and agoraphobia appears to be more idiosyncratic, requiring careful titration of individual doses. Further systematic study seems warranted.

#### REFERENCES

- Zitrin CM, Klein DF, Woerner MG, et al: Treatment of phobias, I: comparison of imipramine hydrochloride and placebo. Arch Gen Psychiatry 1983; 40:125–138
- Zitrin CM, Klein DF, Woerner GM: Treatment of agoraphobia with group exposure in vivo and imipramine. Arch Gen Psychiatry 1980; 37:63-72
- Kahn J, McNair DM, Lipman RS, et al: Imipramine and chlordiazepoxide in depressive and anxiety disorders, II: efficacy in anxious outpatients. Arch Gen Psychiatry 1986; 43: 79–85
- McNair DM, Kahn RJ: Imipramine compared with a benzodiazepine for agoraphobia, in Anxiety: New Research and Changing Concepts. Edited by Klein D, Rabkin JC. New York, Raven Press. 1981
- Marks IM, Gray S, Cohen D, et al: Imipramine and brief therapist-aided exposure in agoraphobics having self-exposure homework. Arch Gen Psychiatry 1983; 40:153–162
- Sheehan DV, Ballenger J, Jacobsen G: Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. Arch Gen Psychiatry 1980; 37:51–59
- Mavissakalian M, Perel J: Imipramine in the treatment of agoraphobia: dose-response relationships. Am J Psychiatry 1985; 142:1032–1036
- Mavissakalian M, Perel JM, Michelson L: The relationship of plasma imipramine and N-desmethylimipramine to improvement in agoraphobia. J Clin Psychopharmacol 1984; 4:36–40
- Ballenger JC, Peterson GA, Laraia M, et al: A study of plasma catecholamines in agoraphobia and the relationship of serum tricyclic levels to treatment response, in Biology of Agoraphobia. Edited by Ballenger JC. Washington, DC, American Psychiatric Press, 1984
- Zitrin CM, Klein DF, Woerner MG: Behavior therapy, supportive psychotherapy, imipramine, and phobias. Arch Gen Psychiatry 1978; 35:307-316
- 11. Jobson K, Linnoila M, Gillam J, et al: Successful treatment of severe anxiety attacks with tricyclic antidepressants: a potential mechanism of action. Am J Psychiatry 1978; 135:863–864
- Nurnberg HG, Coccaro EF: Response of panic disorder and resistance of depression to imipramine. Am J Psychiatry 1982; 139:1060-1062
- Sweeney DR, Gold MS, Pottash ALC, et al: Plasma levels of tricyclic antidepressants in panic disorder. Int J Psychiatry 1983; 13:93-96
- Glassman AH, Perel JM, Shostak M, et al: Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry 1977; 34:197–204
- Reisby N, Gram LF, Bech P, et al: Imipramine: clinical effects and pharmacokinetic variability. Psychopharmacology (Berlin)

1977; 54:263-272

- Walter CJS: Clinical significance of plasma imipramine levels. Proc R Soc Med 1971; 64:282–285
- 17. Olivier-Martin R, Marzin D, Buschsenschutz E, et al: Concentrations plasmatiques de l'imipramine et de la desmethylimipramine et effet anti-dépresseur au cours d'un traitment controlé. Psychopharmacologia 1975; 4:187–195
- Preskorn SH, Weller EB, Weller RA: Depression in children: relationship between plasma imipramine levels and response. J Clin Psychiatry 1982; 43:450–453
- Perel JM, Shostak M, Gann E, et al: Pharmacodynamics of imipramine and clinical outcome in depressed patients, in Pharmacokinetics of Psychoactive Drugs. Edited by Gottschalk

- LA, Merlis S. New York, Spectrum, 1976
- Task Force on the Use of Laboratory Tests in Psychiatry: Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. Am J Psychiatry 1985; 142:155-162
- 21. Jansson L, Ost L: Behavioral treatments for agoraphobia: an evaluative review. Clin Psychol Rev 1982; 2:311-337
- 22. Emmelkamp PMG, Wessels H: Flooding in imagination vs flooding in vivo: a comparison with agoraphobia. Behav Res Ther 1975; 13:7–15
- Garvey MJ, Tuason VB, Johnson RA, et al: Elevated plasma tricyclic levels with therapeutic doses of imipramine. Am J Psychiatry 1984; 141:853–856

# A Family Study of Generalized Anxiety Disorder

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The frequency of generalized anxiety disorder was higher among first-degree relatives of probands with generalized anxiety (N=20) than among the relatives of control subjects (N=20), but it was not higher among relatives of probands with panic disorder (N=40) or agoraphobia (N=40). Also, the frequency of panic disorder was higher among relatives of probands with panic disorder than among control relatives but was not higher among relatives of generalized anxiety probands. Relatives of probands with generalized anxiety who had the same disorder had a mild, stress-related illness. The results confirm the separation between generalized anxiety disorder and panic disorder but challenge the distinction between generalized anxiety and adjustment disorders.

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Generalized anxiety disorder was introduced into DSM-III as a residual category for patients with chronic anxiety symptoms without anxiety attacks.

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The separation of anxiety neurosis into panic disorder and generalized anxiety disorder was based on Klein's observation of anxiety syndromes that appeared differentially responsive to drugs (1). He noticed that imipramine blocked panic attacks but that it did not affect generalized anxiety, the latter being more responsive to benzodiazepines. However, from the time of its inclusion in the new classification, questions were raised about the validity, even the reliability, of this diagnosis. Also, because only about 10% of the anxious patients treated by psychiatrists have generalized anxiety disorder, the illness has received little study (2–4).

Epidemiologic surveys (5, 6) have found generalized anxiety disorder prevalent in the population, and clinical studies have suggested that the disorder can be distinguished from panic disorder. Hoehn-Saric (7, 8) observed fewer somatic symptoms in patients with generalized anxiety, as did Anderson et al. (9), who also found generalized anxiety disorder to have a more gradual onset, a more chronic course, and a more favorable outcome than panic disorder. These authors and Thyer et al. (10) found an earlier age at onset for generalized anxiety than for panic disorder. Although Raskin et al. (11) found these types of patients similar in terms of a number of antecedents, fewer of the generalized anxiety patients had disturbed childhood environments or secondary depression.

Family and twin studies have supported the distinction between generalized anxiety and panic disorder.

Crowe et al. (12) found a higher prevalence of panic disorder among relatives of probands with panic disorder than among control relatives but no difference in the prevalence of generalized anxiety disorder. Similarly, Noyes et al. (13) found similar rates of generalized anxiety disorder among relatives of agoraphobic patients and control relatives, and Cloninger et al. (14) reported that many of the relatives of patients with panic disorder had panic attacks but that relatives of patients with other anxiety disorders did not. Also, Torgersen (15) showed that genetic factors are important in the transmission of panic but not generalized anxiety disorder. He found no difference in the frequency of anxiety disorders among monozygotic and dizygotic twins of probands with generalized anxiety disorder.

Until recently, drug treatment has appeared to distinguish panic and generalized anxiety disorders. The antipanic effect of imipramine has been confirmed in controlled studies, and the drug has a well-established place in the treatment of panic disorder and agoraphobia (16). However, the belief that these disorders are unresponsive to benzodiazepines was challenged by the demonstration of antipanic effects of alprazolam (J. Ballenger et al., unpublished paper, 1985) and diazepam (17). With respect to generalized anxiety, the benzodiazepines have long been considered the standard drug treatment, but Kahn et al. (18) recently found imipramine effective in a large group of volunteers with this disorder. This finding, if confirmed, would further challenge the notion of a differential treatment response.

To test the validity of generalized anxiety disorder we undertook a family interview study. Because the disorder is believed to be heterogeneous, we hypothesized that relatives of persons with the disorder would have a higher frequency of anxiety, affective, and alcohol disorders than control relatives (2, 3). For the purposes of this preliminary study we selected probands with generalized anxiety disorder who had never experienced a panic attack.

#### **METHOD**

Twenty probands with generalized anxiety disorder were recruited through newspaper advertisement. Potential probands were interviewed by a psychiatrist (W.R.Y. or C.M.M.) who administered a structured interview designed to screen for major medical and psychiatric disorders and to emphasize anxiety disorders (13). The diagnosis of generalized anxiety disorder was made according to DSM-III criteria by two psychiatrists (R.R.C. and R.N.) who reviewed the interview data and available medical records. Any subject suspected of ever having had a panic attack was excluded. The mean±SD age of the probands with generalized anxiety disorder was  $44.0\pm14.6$  years; 60.0% were female. Fourteen probands had experienced at least one episode of major depression after the

onset of generalized anxiety, and three had developed alcohol or drug abuse. Fifteen had been treated for their disturbance; four had had psychiatric treatment.

The probands with panic disorder, agoraphobia, and no anxiety disorder had been studied earlier (13). The probands with panic disorder and agoraphobia had been identified through an agoraphobia self-help group and a psychiatric clinic; the control probands had been selected from surgical patients and hospital employees. The percentages of women for the panic disorder, agoraphobic, and control probands were 67.5%, 67.5%, and 75.0%, respectively. The mean± SD ages of the three groups were  $42.7\pm10.7$ ,  $40.2\pm10.4$ , and  $38.1\pm9.4$  years. Secondary depression was diagnosed in 14 panic disorder and 19 agoraphobic probands. Secondary alcohol or drug abuse was identified in three panic disorder probands and 12 agoraphobic probands. Three control probands received psychiatric diagnoses; these were major depression, simple phobia, and adjustment disorder with mixed features.

All available first-degree relatives were interviewed by one of the investigators (C.C.). Relatives within 150 miles were personally interviewed; those living farther away were interviewed by telephone. The same structured interview used with the probands was administered to the relatives (13). The relatives also completed the Brief Symptom Inventory (19), the Fear Survey Schedule (20), and the Personality Diagnostic Questionnaire (PDQ) (21). Family history information on relatives not interviewed was obtained from probands and family members by means of a brief interview schedule that emphasized anxiety, affective, and alcohol disorders.

Diagnoses were made independently by two psychiatrists (R.N. and R.R.C.) after review of all available information. They were made according to DSM-III criteria with certain exceptions. "Probable generalized anxiety disorder" was used for relatives who reported symptoms in only two of the four criterion symptom categories but otherwise met the criteria for generalized anxiety disorder. Relatives who reported one or more panic attacks were assigned a diagnosis of "probable panic disorder." Those whose attacks were accompanied by two or three criterion symptoms but otherwise met the criteria for panic disorder were also given this diagnosis. The family history diagnoses were made according to the Family History Research Diagnostic Criteria (22) except for generalized anxiety disorder, panic disorder, and agoraphobia; these disorders were diagnosed according to the same criteria used for the interviewed subjects. Diagnostic differences were resolved by discussion.

Anxiety disorders were diagnosed in relatives according to the hierarchy outlined in DSM-III. However, the diagnosis of generalized anxiety disorder was reserved for relatives who had never experienced a panic attack. Also, a diagnosis of agoraphobia required definite phobic avoidance. Subjects with panic attacks but no avoidance were diagnosed as having

TABLE 1. Frequency of Psychiatric Disorders in First-Degree Relatives of Control (N=20), Generalized Anxiety (N=20), Panic Disorder (N=40), and Agoraphobic (N=40) Probands

	of C Pro	Relatives of Control Probands (N=113)		Relatives of Generalized Anxiety Probands (N=123)		Relatives of Panic Disorder Probands (N=241)		Relatives of Agoraphobic Probands (N=256)		-Square ialysis	
DSM-III Diagnosis	N	%	N	%	N	%	N	%	(df=3)	p	
Anxiety disorders	15	13.3	37	30.1 <sup>a</sup>	62	25.7	71	27.7	10.98	<.05	
Panic disorder	4	3.5	5	4.1 <sup>b</sup>	36	14.9	18	7.0	20.03	<.001	
Agoraphobia	4	3.5	4	3.3 <sup>b</sup>	4	1.7	24	9.4	17.56	<.001	
Social phobia	1	0.9	1	0.8	4	1.7	9	3.5	_	n.s.	
Simple phobia	2	1.8	2	1.6	4	1.7	7	2.7		n.s.	
Generalized anxiety disorder	4	3.5	24	19.5°	13	5.4	10	3.9	36.58	<.001	
Obsessive-compulsive disorder	0	0.0	1	0.8	0	0.0	2	0.8	_	n.s.	
Other	0	0.0	0	0.0	1	0.4	1	0.4	_	n.s.	
Alcohol disorders	5	4.4	8	6.5	16	6.6	33	12.9	10.51	<.05	
Affective disorders	8	7.1	9.	7.3	10	4.1	12	4.7		n.s.	
Other disorders	4	3.5	9d	7.3	16	6.6	18	7.0	_	n.s.	
All disorders	32	28.3	63	51.2	104	43.2	134	52.3	24.45	<.001	

<sup>&</sup>lt;sup>a</sup>Anxiety disorders (combined) were more frequent among generalized anxiety disorder relatives than control relatives ( $\chi^2=9.68$ , df=1, p< 01).

dIncludes three relatives who had adjustment disorder with anxious mood.

panic disorder. The diagnoses of other anxiety disorders were made according to the predominant symptoms. Where affective or alcohol disorders occurred concomitantly, the disorder that appeared first was considered primary.

#### **RESULTS**

There were 123 first-degree relatives of probands with generalized anxiety who were available for study. The mean±SD age of these relatives was 49.6±20.0 years, and 53.7% were women. Personal interviews were completed with 68.3%, 13.0% refused or were not located, and 18.7% were deceased.

The frequency distributions of psychiatric disorders among the relatives of generalized anxiety, panic disorder, agoraphobic, and control probands are shown in table 1. These percentages are based on probable and definite diagnoses of generalized anxiety disorder, panic disorder, and agoraphobia. Of the 24 relatives of probands with generalized anxiety disorder who also had generalized anxiety, 18 received definite and six received probable diagnoses. The prevalence of anxiety disorders among the relatives of probands with generalized anxiety disorder was higher than that for the control subjects' relatives, just as it had been among the relatives of probands with panic disorder and agoraphobia (13). The higher rate was similar in terms of the proportion affected, but the distribution within the anxiety disorder category was different. A greater proportion of generalized anxiety relatives had generalized anxiety disorder than did the relatives of the control, panic disorder, or agoraphobic probands.

There was no higher frequency of other anxiety disorders, including panic disorder, agoraphobia, or these disorders combined. Among the relatives of the probands with generalized anxiety disorder, a greater proportion of women (24.2%) were diagnosed as having generalized anxiety disorder than men (14.0%).

All of our probands with generalized anxiety disorder met the revised DSM-III criteria (DSM-III-R) for this disorder, although they were not required to do so. As may be seen in table 2, their age and sex distribution were similar to those of the probands with panic disorder and agoraphobia, but these probands had an earlier and more gradual onset than those with panic disorder or agoraphobia. Like the panic disorder and agoraphobic probands, about a quarter of those with generalized anxiety disorder reported a remitting course (symptom-free intervals of at least 3 months). However, all but two claimed to have been symptomatic a majority of the time since the onset of the disorder, a median of 22.5 years earlier. A greater proportion of probands with generalized anxiety had experienced secondary depression and were symptomatic at the time of the interview.

The relatives of the probands with generalized anxiety disorder who were identified as having the same disorder shared the symptoms of anxious expectation, vigilance and scanning, motor tension, and autonomic hyperactivity. However, as may be seen in table 3, they were older at illness onset than the probands and had a significantly shorter median duration of illness. They also differed from the probands in that more of them had remissions, fewer had secondary depression, and fewer reported abnormal personality traits. Half of

p<.01). <sup>b</sup>The combined total of panic disorder and agoraphobia was higher for panic disorder relatives than generalized anxiety disorder relatives  $(\chi^2=6.02, df=1, p<.05)$ .

Generalized anxiety disorder was more frequent among generalized anxiety disorder relatives than control relatives ( $\chi^2=14.37$ , df=1, p<.001).

TABLE 2. Clinical Features of Probands With Generalized Anxiety Disorder, Panic Disorder, and Agoraphobia

	Anxiety	eralized Probands =20) <sup>b</sup>	Pro	Disorder bands =40) <sup>b</sup>	Pro	aphobic bands =40) <sup>b</sup>	Chi-Squar	e Analysis
Feature <sup>a</sup>	N	%	N	%	N	%	(df=2)	P
Female	12	60.0	27	67.5	27	67.5	W-100-00	n.s.
Sudden onset	1	5.0	15	41.7	28	70.0	23.09	<.005
Precipitating events	16	80.0	24	66.7	23	57.5	*****	n.s.
Premorbid anxious traits	8	40.0	12	34.3	20	50.0	*******	n.s.
Unremitting course	15	<i>75</i> .0	23	65.7	31	77.5	*****	n.s.
Secondary depression	14	70.0	14	35.0	19	47.5	6.56	<.05
Secondary alcohol abuse	3	15.0	3	7.5	12	30.0	7.01	<.05
Symptomatic at time of interview	20	100.0	29	80.6	38	95.0	7.27	<.05
Taking medication at time of interview	9	45.0	17	47.2	28	70.0		n.s.

<sup>&</sup>lt;sup>a</sup>The mean±SD ages of the three groups were 44.0±14.6, 42.7±10.7, and 40.2±10.4 years, respectively. Their mean±SD ages at onset were 19.2±11.9, 28.0±10.8, and 23.9±8.2 years (F=5.01, df=2, 93, p<.01; data not available for four panic disorder probands). bIn a few instances sample size is less than the figure shown because of incomplete data.

TABLE 3. Clinical Features of Probands With Generalized Anxiety Disorder and Their Relatives With the Same Diagnosis

		bands		atives	Chi-Square Analysis <sup>c</sup>		
	(17)	$\frac{(=20^{6})}{}$	(14:	$=24^{\rm b}$ )	$\chi^2$		
Feature <sup>a</sup>	N	%	N	%	(df=1)	р	
Female	12	60.0	16	66.7		n.s.	
Sudden onset	1	5.0	7	36.8	4.26	<.02	
Precipitating stressor of at least moderate severity	14	70.0	16	84.2	wasse	n.s.	
Abnormal personality traits	14	73.4	7	35.0	5.12	<.05	
Unremitting course	15	75.0	4	20.0	7.40	<.01	
Secondary depression	14	70.0	5	20.8	8.84	<.005	
Ever treated	15	75.0	12	50.0	***************************************	n.s.	
Symptomatic at time of interview	20	100.0	9	47.4	14.16	<.001	

<sup>&</sup>lt;sup>a</sup>The mean±SD ages of the probands and relatives were 44.0±14.6 and 48.4±18.2 years, respectively. Their ages at onset of illness were 19.2±11.9 and 31.2±12.8 years (t=2.92, df=37, p<.01), and their median durations of illness were 12.5 and 1.0 years (longest episode of illness for each patient was used to calculate median duration of illness).

these relatives had received treatment at some time, and nearly half reported symptoms at the time of interview. Of the 27 symptomatic periods described by the interviewed relatives, 24 were judged to have been precipitated by events or circumstances that were responsible for continuing symptoms. When all stressors were rated according to the *DSM-III* severity scale, 70.4% were judged to have been at least severe and 85.1% were at least moderate.

Roughly a third (36.8%) of the probands with generalized anxiety disorder were identified as having DSM-III personality disorders on the basis of the PDQ. An additional third (36.8%) met the criteria in terms of traits but scored below the cutoff for a disorder on the impairment/distress scale. Dependent personality was identified most often among the probands. By contrast, only 15.0% of their relatives with generalized anxiety were identified by the PDQ as having personality disorders, and an additional 20.0% met the criteria for traits. The mean impairment/distress score for the probands was 1.7, compared to 1.1 for their relatives with generalized anxiety disorder. Among relatives with no diagnoses, 3.4% had personality disorders and 10.3% had abnormal traits;

they had a mean score of 0.5 on the impairment/distress scale.

#### **DISCUSSION**

Our results are preliminary and should be interpreted with caution. In the first place, we cannot be completely confident of the diagnosis of generalized anxiety disorder, since the reliability of this category has not been established (2–4). Second, because the diagnoses were not made blindly, it is possible that interviewer bias affected the observed frequency of some disorders (14). Third, because we studied a small number of families, we may have failed to detect real differences in the frequency of disorders among relatives. Finally, our probands with generalized anxiety disorder were community volunteers, whereas those with panic disorder were medical outpatients (23). The different methods of selection may have influenced our results.

We confirmed that a substantial proportion of anxious volunteers from the general population meet criteria for generalized anxiety disorder (23). Our

<sup>&</sup>lt;sup>b</sup>In some instances sample size is less than the figure shown because of incomplete data.

<sup>&</sup>lt;sup>c</sup>Chi-square tests were done with Yates' correction.

probands were selected on the basis of DSM-III criteria, but they also met the more stringent criteria of DSM-III-R. Two features of their illnesses were striking, the first being the perceived importance of psychosocial stressors. Some probands reported that a single stressor was present for years, while others linked a succession of stressful circumstances to persisting symptoms. The second feature was the frequency of personality disturbances. According to a liberal scoring of the PDQ, more than two-thirds qualified for axis II diagnoses.

Our results suggest that generalized anxiety disorder is separate from panic disorder. The distribution of anxiety disorders among the families studied supports this conclusion. Among the relatives of probands with generalized anxiety disorder, there was a higher frequency of generalized anxiety than among the relatives of the control, panic disorder, and agoraphobic probands. Also, the high frequency of panic disorder among the relatives of the panic disorder probands and the high frequency of agoraphobia among the relatives of the agoraphobic probands were not seen in the generalized anxiety disorder families. In fact, apart from the high frequency of generalized anxiety disorder, the families of the probands with generalized anxiety disorder were no different from those of the control subjects. These findings support phenomenologic, family, and treatment studies that point toward separate disorders (1–3, 7–16).

Our findings also suggest that generalized anxiety disorder may be difficult to distinguish from adjustment disorder with anxious mood. All of the relatives with generalized anxiety met the DSM-III criteria for generalized anxiety disorder, but only 43% met the more stringent criteria of DSM-III-R. The others had fewer than six criterion symptoms, an illness of less than 6 months' duration, or both. On the whole, the disturbances were relatively mild, brief, and clearly related to psychosocial stressors. Disturbances of this type appear to belong in an adjustment disorder category (24, 25).

Thus, the separation between generalized anxiety disorder and panic disorder may be valid, but the distinction between generalized anxiety and adjustment disorders may not. In DSM-III this distinction is based on the number and duration of symptoms as well as the relationship to a psychosocial stressor. This relationship is difficult to assess because it involves not only the nature and severity of the stressor but also the severity and duration of the reaction and premorbid vulnerability. Given the number and chronicity of symptoms, it would be difficult to say that our probands suffered from simple adjustment reactions. Also, the stressors associated with the onset of their disturbances occurred many years earlier and did not differ from those reported by the probands with panic disorder or agoraphobia. A solution might be to drop the adjustment disorder category and, in accord with the multiaxial system of DSM-III, record psychosocial stressors on a separate axis.

When we compared probands with generalized anxiety disorder, panic disorder, and agoraphobia, we found differences in clinical features and natural history that support the separation of these illnesses. First of all, the probands with generalized anxiety disorder had experienced fewer autonomic symptoms. This finding, along with earlier reports (7-9), suggests that persons with generalized anxiety disorder do not share the autonomic instability of patients with panic disorder. Also, consistent with previous reports (9, 10), we found the probands and relatives with generalized anxiety disorder to have had an earlier and more gradual onset of illness. Although the generalized anxiety probands differed little from those with panic disorder or agoraphobia in terms of course, more of them reported one or more episodes of secondary depression, confirming an earlier finding (9). Judging from the relatives with generalized anxiety disorder, the illness may be even milder than our comparison of probands suggests. In fact, patients with this disorder in primary care settings appear to have a remitting course (26).

We observed no difference in the frequency of affective disorders between the relatives of generalized anxiety disorder probands and relatives of control subjects. Consequently, we found no evidence for a relationship between generalized anxiety and major depression despite the finding of secondary depression in many of our probands. This finding is consistent with earlier family studies (12–14) in which we found no increase in the frequency of major depression among relatives of probands with panic disorder or agoraphobia. On the other hand, Leckman et al. (27) found a high rate of both generalized anxiety disorder and major depression among the relatives of depressed probands who also met criteria for generalized anxiety disorder. Reviewing this and other data, Breier et al. (3) suggested that a relationship between anxiety and depression might exist. We were not able to demonstrate such a relationship.

Our results suggest that a personality predisposition to generalized anxiety disorder may exist. Relatives with this disorder more frequently met the trait criteria for DSM-III personality disorders than did relatives with no axis I disorder (35.0% versus 13.7%, respectively). Also, the fact that a high proportion of probands with generalized anxiety disorder met the trait criteria for personality disorders points to a link between personality disturbance and generalized anxiety. However, the frequency of such disturbances appears similar to that found in patients with panic disorder. Using the PDQ, Reich et al. (28) found 34.2% of patients with panic disorder to have personality disorders, compared to 36.8% of our generalized anxiety probands. In both groups dependent personality disorder was the most common disturbance found.

#### **REFERENCES**

1. Klein DF: Delineation of two drug responsive anxiety syndromes. Psychopharmacologia 1964; 5:397–408

- Barlow DH, Blanchard EB, Vermilyea JA, et al: Generalized anxiety and generalized anxiety disorder: description and reconceptualization. Am J Psychiatry 1986; 143:40

  –44
- 3. Breier A, Charney DS, Heninger GR: The diagnostic validity of anxiety disorders and their relationship to depressive illness. Am J Psychiatry 1985; 142:787-797
- DiNardo PA, O'Brien GT, Barlow DH, et al: Reliability of DSM-III anxiety disorder categories using a new structured interview. Arch Gen Psychiatry 1983; 40:1070–1075
- Uhlenhuth EH, Balter MB, Mellinger GD, et al: Symptom checklist syndromes in the general population: correlations with psychotherapeutic drug use. Arch Gen Psychiatry 1983; 40: 1167–1173
- Weissman MM: The epidemiology of anxiety disorders: rates, risks, and family patterns, in Anxiety and the Anxiety Disorders. Edited by Tuma AH, Maser JD. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985
- 7. Hoehn-Saric R: Characteristics of chronic anxiety patients, in Anxiety: New Research and Changing Concepts. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
- 8. Hoehn-Saric R: Comparison of generalized anxiety disorder with panic disorder patients. Psychopharmacol Bull 1982; 18: 104-108
- Anderson DJ, Noyes R Jr, Crowe RR: A comparison of panic disorder and generalized anxiety disorder. Am J Psychiatry 1984; 141:572–575
- Thyer BA, Parrish RT, Curtis GC, et al: Ages of onset of DSM-III anxiety disorders. Compr Psychiatry 1985; 26:113– 122
- Raskin M, Peeke HVS, Dickman W, et al: Panic and generalized anxiety disorders: developmental antecedents and precipitants. Arch Gen Psychiatry 1982; 39:687–689
- 12. Crowe RR, Noyes R, Pauls DL, et al: A family study of panic disorder. Arch Gen Psychiatry 1983; 40:1065–1069
- Noyes R Jr, Crowe RR, Harris EL, et al: Relationship between panic disorder and agoraphobia: a family study. Arch Gen Psychiatry 1986; 43:227–233
- 14. Cloninger CR, Martin RL, Clayton P, et al: A blind follow-up and family study of anxiety neurosis: preliminary analyses of the St Louis 500, in Anxiety: New Research and Changing Concepts. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
- 15. Torgersen S: Genetic factors in anxiety disorders. Arch Gen

- Psychiatry 1983; 40:1085-1089
- Noyes R Jr: Psychopharmacology of phobic disorders, in Drugs in Psychiatry, vol 4. Edited by Burrows GD, Norman TR, Davies B. New York, Elsevier, 1987
- 17. Noyes R Jr, Anderson DJ, Clancy J, et al: Diazepam and propranolol in panic disorder and agoraphobia. Arch Gen Psychiatry 1984; 41:287–292
- Kahn RJ, McNair DM, Lipman RS, et al: Imipramine and chlordiazepoxide in depressive and anxiety disorders, II: efficacy in anxious outpatients. Arch Gen Psychiatry 1986; 43: 79–85
- Derogatis LR: Brief Symptom Inventory. Baltimore, Johns Hopkins University School of Medicine, Clinical Psychometric Research, 1982
- 20. Hallam RS, Hafner RJ: Fears of phobic patients: factor analyses of self-report data. Behav Res Ther 1978; 16:1-6
- 21. Hyler S, Reider R, Spitzer R, et al: Personality Diagnostic Questionnaire (PDQ). New York, New York State Psychiatric Institute, 1983
- Andreasen NC, Endicott J, Spitzer RL, et al: The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235
- 23. Barrett J: Psychiatric diagnoses (Research Diagnostic Criteria) in symptomatic volunteers. Arch Gen Psychiatry 1981; 38:153–157
- Looney JG, Gunderson EKE: Transient situational disturbances: course and outcome. Am J Psychiatry 1978; 135:660–663
- Andreasen NC, Hoenk PR: The predictive value of adjustment disorders: a follow-up study. Am J Psychiatry 1982; 139:584– 590
- Kessler LG, Cleary PD, Burke JD: Psychiatric disorders in primary care: results of a follow-up study. Arch Gen Psychiatry 1985; 42:583–587
- 27. Leckman JF, Weissman MM, Merikangas KR, et al: Panic disorder and major depression: increased risk of depression, alcoholism, panic, and phobic disorders in families of depressed probands with panic disorder. Arch Gen Psychiatry 1983; 40: 1055-1060
- 28. Reich J, Noyes R Jr, Troughton E: Dependent personality disorder associated with phobic avoidance in patients with panic disorder. Am J Psychiatry 1987; 144:323-326

# Reduced Length and Cost of Hospital Stay for Major Depression in Patients Treated With ECT

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To investigate the effect of treatment modality on length of hospital stay, the authors retrospectively studied 86 admissions of 74 patients with major depression. All 19 patients who received ECT recovered, in contrast to only 27 (49%) of 55 patients given tricyclic antidepressants or other medication. The 28 patients who had not responded to antidepressants recovered after treatment with ECT. Treatment modality had a highly significant effect on length of hospital stay: patients given ECT stayed a mean of 13 fewer days, saving more than \$6,400 per patient at current rates. These findings of significant economic and therapeutic benefits in the use of ECT raise issues about treatment selection for depressed inpatients.

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D uration of hospital stay becomes increasingly important as economic pressures on medicine mount. Although several authors (1–5) have urged cost-benefit analyses for psychiatric treatments, few studies have examined the cost and relative efficacy of treatments. In this retrospective study we assessed the effects of ECT and tricyclic antidepressants on outcome and length of hospital stay for patients with major depression.

Previous studies (6–8) demonstrated the efficacy of ECT for inpatients with major depression, showing it to be equal or superior to antidepressant medication. It is the treatment of choice for delusional depression: recovery rates of 82%–100% have been reported (8–15). It is also the treatment of choice for patients who do not respond to antidepressant medication (7), for

depressed patients at high risk for suicide (6), and for patients with severe endogenous depression (7). Nevertheless, ECT remains a highly controversial treatment (7).

Few studies have considered length of hospital stay as a variable in the choice of treatment for affective disorder. Several studies have shown that patients given ECT had shorter lengths of stay than untreated control subjects (6). In 1965 Bratfos and Haug (16) found a shorter length of stay for ECT-treated patients with bipolar disorder than for those who received medication, and Avery and Winokur (17) found similar results 12 years later. Babigian and Guttmacher (18) found a longer length of stay for ECT-treated than for drug-treated patients with affective disorder, although their state hospital population may have been more heterogeneous. Hordern et al. (19) found no difference in length of stay between patients given ECT and patients who responded to tricyclic antidepressants but a significantly longer stay for patients who did not respond to tricyclic antidepressants. Perry et al. (11) found that patients with delusional depression had shorter hospital stays and better response with ECT than with tricyclic antidepressants and neuroleptics.

Indiscriminate past use, misinformation, and fear of electrical therapy have at times relegated ECT to a secondary treatment status and, in some locales (20–22), have curtailed its use entirely. ECT is underused despite its demonstrated effectiveness in the treatment of affective disorder (6, 10). In this era of cost containment and limited insurance, demonstration of the economic incentives and superior clinical efficacy of ECT would assist clinicians and patients in choosing between treatment modalities as well as overcoming prejudice against ECT.

#### **METHOD**

We reviewed the charts of all patients admitted to the Psychobiological Research Unit of the Payne Whitney Psychiatric Clinic who met Research Diagnostic Criteria (RDC) (23) for major depressive disorder for whom data had been collected in connection with other studies of affective disorder (13, 24–27) during

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the periods June 1977 to June 1980 and June 1982 to June 1984. Having excluded patients with bipolar and schizoaffective disorders, patients with substantial medical illness, and those who had received more than one trial of antidepressant medication, we identified 74 patients who had been treated with ECT alone, who had been treated with tricyclic antidepressants alone, or who had received ECT after not responding to a trial of tricyclic antidepressants. We also noted all subsequent hospitalizations of these 74 patients at our clinic; there were 86 such admissions.

The data collected included age, sex, type of insurance, history of depression, number of previous hospitalizations, history of ECT, family history of depression, presence of psychosis, suicide attempts immediately before admission, and admission Hamilton Rating Scale for Depression scores. For patients who had not responded to tricyclic antidepressants, length of stay was subdivided into days when tricyclics were given and days when ECT was given. We included a minimum of 2 days for ECT workup as part of the ECT treatment period. So as not to favor ECT, we counted the entire stay from the start of the pre-ECT workup as ECT days, even when this period included the starting of discharge medications or an extended wait for placement. We calculated the cost of stay at the current rate of \$485/day. Additional measures of the actual in-hospital cost of stay included number of medical consultations, days of maximum observation, and incident reports for each patient. These indexes provided data on the intensity of staff involvement with the patient. Outcome was assessed by clinical global improvement (CGI) ratings, relapse rates at 6 months and 1 year of follow-up after discharge, and discharge medications (or maintenance ECT).

All subjects met RDC for major unipolar depression, with or without the endogenous subtype, during their index admission. One week after admission, patients were rated on the 24-item Hamilton depression scale and were included in the study if their score exceeded 20. ECT was given three times a week and was bilateral except in one instance. Adequate trials of tricyclic antidepressants were defined as at least 3 weeks at 150 mg of imipramine, amitriptyline, desipramine, or doxepin or combined plasma levels of imipramine and desipramine (or amitriptyline) greater than 240 ng/ml. For nortriptyline, at least 3 weeks of treatment and a blood level of 50-150 ng/ml were required. Doses of tricyclic antidepressants other than nortriptyline were raised to 300 mg/day unless this was precluded by side effects. Eighteen patients received desipramine, 17 received amitriptyline, 15 received imipramine, two received doxepin, and one received nortriptyline. Also included among patients given tricyclic antidepressants were one patient treated with trazodone, 600 mg/day, and another who received only haloperidol, 30 mg/ day, for psychotic depression. Both of these patients were in the group who were given ECT after not responding to medication. Some patients treated with tricyclic antidepressants also received neuroleptics.

TABLE 1. Length of Hospital Stay of Patients With Major Depression Given ECT Only, Tricyclic Antidepressants Only, or ECT After Not Responding to Tricyclic Antidepressants

	Length (day	
Group	Mean	SD
Patients given ECT only (N=19) <sup>b</sup>	41.4 <sup>c</sup>	15.6
Delusional (N=9)	39.7	14.3
Nondelusional (N=10)	43.0	17.3
All patients given tricyclic antidepressants		
$(N=55)^{d}$	54.6	24.8
Patients given tricyclic antidepressants only		
(N=27)	37.5	11.9
Delusional (N=2)	46.0	21.2
Nondelusional (N=25)	36.8	11.3
Patients given ECT after not responding to		
tricyclic antidepressants (N=28)	71.0°	23.0
While given tricyclic antidepressants	38.9	16.1
While given ECT	32.1	14.3
Delusional (N=13)	64.0	24.7
While given tricyclic antidepressants	32.8	16.5
While given ECT	31.1	16.1
Nondelusional (N=15)	77.1	20.1
While given tricyclic antidepressants	44.2	14.3
While given ECT	32.9	13.1

<sup>a</sup>Treatment modality had a significant effect on length of stay (F=28.5, df=2, 71, p<.00001).

bThe mean cost of hospitalization at \$485/day in 1986 was \$20,079. ct=2.7, df=50, p<.01 (patients given ECT only compared with all patients given tricyclic antidepressants). The mean cost of hospitalization at \$485/day in 1986 was \$26,481.

<sup>d</sup>The mean cost of hospitalization at \$485/day in 1986 was \$26,481 <sup>c</sup>p<.05, Tukey-B procedure.

Response to ECT or medication was defined as a posttreatment Hamilton score of less than 10. Partial response was defined as a reduction in Hamilton score by 50% or to between 10 and 20. Failure to respond to treatment was defined as a Hamilton score greater than 20 after an adequate trial and the decision that an alternative treatment was needed.

# RESULTS

Nineteen patients received ECT only. All of these patients responded with resolution of their depression. Fifty-five patients were given tricyclic antidepressants. Only 27 (49%) of these patients responded. The remaining 28 patients given tricyclic antidepressants were then given ECT, to which all 28 responded. Treatment modality had a significant effect on length of hospital stay (table 1). Post hoc analysis revealed no difference in length of stay between patients given ECT only and patients given tricyclic antidepressants only but a significant difference between these two groups and patients given ECT after not responding to medication (table 1). We compared the 55 patients given tricyclic antidepressants with the 19 given ECT only to assess the effect of initial assignment of treatment modality. The patients given ECT only had a significantly shorter length of stay than the patients given tricyclic antidepressants (table 1).

The 55 patients given tricyclic antidepressants and

TABLE 2. Characteristics at Admission of Patients Given ECT Only, Tricyclic Antidepressants Only, or ECT After Not Responding to Tricyclic **Antidepressants** 

	A	re		S	ex			Histo Depre				tory	Previ Hospi		Ç.,;	.cide	Hami Depre	
	Age (years)		M I		F		Personal		Family		$CT^a$	izations		Attempts		Scoreb		
Group	Mean	SD	N	%	N	%	N	%	N	%	N	%	Mean	SD	N	%	Mean	SD
Patients given ECT only (N=19) Patients given tricyclic antidepressants only	64.7	13.8	7	37	12	63	15	79	18	95	15	79	1.5	1.2	3	16	32.3	9.1
(N=27) Patients given ECT after not responding to tricyclic	56.7	13.0	6	22	21	78	16	59	20	74	8	30	1.0	1.3	4	15	30.3	6.9
antidepressants (N=28)	62.2	14.2	9	32	19	68	22	79	22	79	16	57	1.4	1.5	3	11	36.2	9.4

a Significantly more patients in the two groups who were given ECT had a history of ECT ( $\chi^2$ =9.2, df=2, p<.02).

TABLE 3. Characteristics of Hospitalization of Patients Given ECT Only, Tricyclic Antidepressants Only, or ECT After Not Responding to Tricyclic Antidepressants

	Med Consulta		Maximum (da		Incident Reports <sup>b</sup>		
Group	Mean	SD	Mean	SD	Mean	SD	
Patients given ECT only (N=19) Patients given tricyclic antidepressants only (N=27) Patients given ECT after not responding to tricyclic	2.2 1.3	1.1 1.4	5.7 5.8	9.6 26.3	.00	.00	
antidepressants (N=28)	2.3	1.7	29.1	67.3	.39	1.2	

the 19 given ECT only did not differ significantly in age, sex, personal or family history of depression, type of insurance, suicide attempts before admission, number of previous hospitalizations, number of medical consultations during hospitalization, or number of days of maximum observation (tables 2 and 3). The groups differed in severity of illness as measured by admission Hamilton scores (table 2). They also differed in number of incident reports (table 3). They did not differ in frequencies of known relapses at 6 and 12 months. Patients who received tricyclic antidepressants only and patients given ECT after not responding to tricyclic antidepressants did not differ in medication dose. The former group received 229 mg/day (range= 75-300 mg/day), and the latter received 228 mg/day (range=100-300 mg/day). Each group of patients given ECT received a mean of eight treatments.

More patients given only ECT had a history of previous ECT (table 2). Fewer of the patients given only tricyclic antidepressants were delusional than patients given ECT only or ECT after not responding to tricyclic antidepressants ( $\chi^2$ =10.0, df=2, p=.04). More patients given only ECT were discharged without medication than were all patients given tricyclic antidepressants ( $\chi^2=5.2$ , df=1, p<.05). Calculating hospital costs at the 1986 rate of \$485/day, we found that the cost of stay averaged \$20,079 for the patients given ECT only and \$26,481 for all patients given tricyclic antidepressants, yielding an average net saving of \$6,402 for ECT.

There were significantly more psychotic patients in the groups given ECT only or ECT after not responding to tricyclic antidepressants than in the group given tricyclic antidepressants only ( $\chi^2=10.0$ , df=2, p= .04). Psychotic depression responds preferentially to ECT rather than to tricyclic antidepressants (17), so patients with psychotic depression in the groups of patients given tricyclic antidepressants might have biased our length of stay findings in favor of ECT. When only the 24 nondelusional patients were considered, the length of stay for the 10 patients treated only with ECT remained shorter but the difference did not reach significance (table 1). The 15 nondelusional patients given ECT after not responding to tricyclic antidepressants were significantly older than the 25 nondelusional patients who received tricyclic antidepressants only  $(64.9\pm13.2 \text{ versus } 55.4\pm12.5 \text{ years};$ F=3.7, df=2, 47, p=.03). However, 15 nondelusional patients required ECT after not responding to tricyclic antidepressants and therefore incurred greater length of stay (table 1). They also required more medical consultations and incident reports but were no more ill as measured by admission Hamilton score (t=0.3,df=38, p<.8). Calculated at the 1986 rate of S485/day for hospitalization, the saving of 9 days for a nondelusional patient treated with ECT was worth \$4,365.

bSignificant differences between groups (F=3.1, df=2, 55, p<.05); patients given tricyclic antidepressants only were significantly less depressed than those given ECT after not responding to tricyclic antidepressants (p<.05, Tukey-B procedure).

a Significant difference between groups (F=4.1, df=2, 73, p<.02). b Significant differences between groups (F=3.1, df=2, 73, p<.005); patients given ECT only and patients given tricyclic antidepressants only had significantly fewer incident reports than patients given ECT after not responding to tricyclic antidepressants (p<.05, Tukey-B procedure).

A subgroup of seven patients had at least one admission for ECT alone and one admission for tricyclic antidepressant treatment. In every case, the ECT-only admission was shorter. A paired t test showed that length of stay was shorter for admissions where the only treatment was ECT (t=3.1, df=6, p<.05).

#### **DISCUSSION**

To our knowledge, this is the first study of length of inpatient stay and treatment modality in major depression. Patients treated initially with ECT had a shorter length of stay than the patients given tricyclic antidepressants despite comparable severity of illness. The average saving of 13 hospital days—\$6,405—with ECT has substantial economic import. In addition to costing less in terms of hospital and medical costs and patients' loss of income while hospitalized, ECT provided relief from the suffering and morbidity associated with 13 days of illness and hospitalization per patient. The cost differential would have been further compounded by patients who failed multiple drug trials before receiving ECT treatment; we excluded such patients from this study.

Like the report of Hordern et al. (19), our study found no significant difference between patients who responded to either ECT or tricyclic antidepressants but a significant difference between these two groups and patients who did not respond to tricyclic antidepressants. In terms of demands on staff time, the treatment groups did not differ in medical consultations or in days of maximum observation. Incident reports were more frequent for patients who did not respond to medication than for ECT-only patients, suggesting that the more prompt recovery of ECT patients limited the opportunity for accidents and avoided medication-induced orthostatic hypotension. Maximum observation and incident reports were most frequent in the group of medication nonresponders but least common in the ECT-only group, particularly after the first week of treatment.

Our data are consistent with results of previous studies that have shown ECT to be superior to tricyclic antidepressants in treating delusional depression (6, 8–17, 28). Our findings also indicate that ECT is no less effective than tricyclic antidepressants and possibly more so in the treatment of nondelusional depression. The response rate of our patients to medication is comparable to that found in other inpatient studies (9, 22, 24, 26, 28). ECT response rates of 100% have been reported (14, 15), but ECT treatment failures could be expected in a larger series of patients. ECT was equally effective as an initial treatment and for patients who had not responded to medication.

Limitations of this study are its retrospective design and focus on short-term outcome. Although retrospective design opens this study to the criticism of selection bias and limits its generalizability, we found little evidence for systematic bias beyond an association of good previous response to ECT with the selection of further ECT. Patients who did not respond to tricyclic antidepressants received adequate trials of medication. Length of stay data may indeed have been weighted against ECT in this study. Patients given ECT only and those who received ECT after not responding to tricyclic antidepressants were given a mean of eight ECTs, but length of stay for ECT was considerably longer for the former group (41.4 days versus 32.1 days). Perhaps ECT-only patients had extended hospital stays to allow for resolution of organicity, whereas insurance constraints hastened discharge of the latter group. This bias against the ECT-only group makes the findings for ECT more impressive.

ECT should be considered more frequently as the treatment of choice in depression for delusional patients, patients at high risk for suicide, older patients who do not tolerate the side effects of tricyclic antidepressants or are poorly responsive by history, more severely depressed patients without delusions, and those with limited insurance coverage. The efficacy of ECT should be considered when discussing treatment alternatives and financial considerations with patients and their families. Economics is, however, only one of many factors influencing the clinical choice of treatment (1, 3, 4). Further prospective studies are urgently required to clarify the factors predicting nonresponse to tricyclic antidepressants and response to ECT so that clinicians may assign patients initially to the most effective treatment.

# REFERENCES

- Pincus HA: Making the case for consultation-liaison psychiatry: issues in cost-effectiveness analysis. Gen Hosp Psychiatry 1984; 6:173-179
- Pardes H, Pincus HA: Challenges to academic psychiatry. Am J Psychiatry 1983; 140:1117–1126
- 3. Frank R: Cost-benefit analysis in mental health services: a review of the literature. Administration in Mental Health 1981; 8.61-76
- 4. Panzetta AF: Cost benefit studies in psychiatry. Compr Psychiatry 1973; 14:451–455
- Glass NJ, Goldberg D: Cost benefit analysis and the evaluation of psychiatric services. Psychol Med 1977; 7:701–707
- Fink M: Convulsive Therapy: Theory and Practice. New York, Raven Press, 1979
- Electroconvulsive Therapy: Consensus Development Conference Statement. National Institutes of Health Consensus Development Conference Statement 1985; 5(11)
- Avery D, Lubrano A: Depression treated with imipramine and ECT: the DeCarolis study reconsidered. Am J Psychiatry 1979; 136:559-562
- 9. DeCarolis V, Giberti F, Roccatagliata G, et al: [Imipramine and electroshock in the treatment of depression: a clinical statistical analysis of 437 cases.] Sist Nerv 1964; 16:29–42 (Italian)
- Charney DS, Nelson JC: Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry 1981; 138:328–333
- Perry PJ, Morgan DE, Smith RE, et al: Treatment of unipolar depression accompanied by delusions. J Affective Disord 1982; 4:195-200
- 12. Glassman AH, Kantor SJ, Shostak M: Depression, delusions, and drug response. Am J Psychiatry 1975; 132:716-719
- 13. Brown RP, Frances A, Kocsis JH, et al: Psychotic vs nonpsy-

- chotic depression: comparison of treatment response. J Nerv Ment Dis 1982; 170:635-637
- 14. Minter RE, Mandel MR: The treatment of psychotic major depressive disorder with drugs and electroconvulsive therapy. J Nerv Ment Dis 1979; 167:726-733
- 15. Kaskey GB, Nasr S, Meltzer HY: Drug treatments in delusional depression. Psychiatry Res 1980; 1:267-277
- 16. Bratfos O, Haug JO: Electroconvulsive therapy and anti-depressant drugs in manic-depressive disease. Acta Psychiatr Scand 1965; 41:588-596
- 17. Avery D, Winokur G: The efficacy of electroconvulsive therapy and anti-depressants in depression. Biol Psychiatry 1977; 12:
- 18. Babigian HM, Guttmacher LB: Epidemiologic considerations in electroconvulsive therapy. Arch Gen Psychiatry 1984; 41:246-
- 19. Hordern A, Burt CG, Holt NF: Depressive States. Springfield,
- Ill, Charles C. Thomas, 1965

  20. Mills MJ, Pearsall DT, Yesavage JA, et al: Electroconvulsive therapy in Massachusetts. Am J Psychiatry 1984; 141:534-538
- Winslade WJ, Liston EH, Ross JW, et al: Medical, judicial, and statutory regulation of ECT in the United States. Am J Psychi-

- atry 1984; 141:1349-1355
- 22. Kramer BA: Use of ECT in California, 1977-1983. Am J Psychiatry 1985; 142:1190-1192
- 23. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Disorders, 3rd ed, updated. New York, New York State Psychiatric Institute, Biometrics Research, 1981
- 24. Brown RP, Sweeney J, Loutsch E, et al: Involutional melancholia revisited. Am J Psychiatry 1984; 141:24-28
- 25. Brown RP, Sweeney J, Frances A, et al: Age as a predictor of treatment response in endogenous depression. J Clin Psychopharmacol 1983; 3:176-178
- 26. Kocsis JH, Hanin I, Bowden C, et al: Imipramine and amitriptyline concentrations and clinical response in major depression. Br J Psychiatry 1986; 148:52-57
- 27. Butler TA, Kocsis JH, Kutt H: Tricyclic blood levels and clinical response, in CME Syllabus and Scientific Proceedings in Summary Form, 134th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1981
- 28. Roose SP, Glassman AH, Walsh BT, et al: Tricyclic nonresponders: phenomenology and treatment. Am J Psychiatry 1986; 143:

# Neurobiological Mechanisms of Panic Anxiety: Biochemical and Behavioral Correlates of Yohimbine-Induced Panic Attacks

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The effects of vohimbine, an  $\alpha_2$ -adrenergic receptor antagonist, on anxiety, blood pressure, heart rate, and plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and cortisol were determined in 20 healthy subjects and 68 patients who had agoraphobia with panic attacks or panic disorder. Yohimbine produced panic attacks meeting DSM-III criteria in 37 patients and one healthy subject. The patients reporting yohimbine-induced panic attacks had significantly larger increases in plasma MHPG, cortisol, systolic blood pressure, and heart rate than the healthy subjects. These findings support the hypothesis relating high noradrenergic neuronal activity to the pathophysiology of panic attacks in a subgroup of panic disorder patients.

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A considerable body of preclinical data indicates that increased activity of brain noradrenergic neurons is involved in the development of anxiety or fear (1, 2). Neuroanatomical and neurophysiological studies of the noradrenergic system provide a basis for relating increased activity of this system to the behavioral expression of anxiety and fear and the somatic symptoms and cardiovascular changes that accompany severe anxiety states (1–7).

Recent clinical investigations suggest that a subgroup of patients with panic disorder may exhibit abnormalities in the regulation of noradrenergic function. Yohimbine, which activates noradrenergic neu-

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rons by blocking the  $\alpha_2$ -adrenergic autoreceptor, has been shown to produce greater increases in anxiety, somatic symptoms, blood pressure, and plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in panic disorder patients than in healthy subjects (2). The abnormal responses to yohimbine in patients with panic disorder are consistent with findings of an abnormally low number of platelet  $\alpha_2$ -adrenergic receptor binding sites in patients with panic disorder (8, 9). These observations suggest that episodic increases in noradrenergic neuronal function may be related to the cause of spontaneous and phobic-stimulus-induced panic attacks.

The purpose of the present investigation was to further evaluate the relationship between the regulation of noradrenergic function and the development of panic anxiety states. To extend a previous study (2), the effects of yohimbine on plasma MHPG level, cortisol level, blood pressure, heart rate, and anxiety were determined in an additional 29 patients, resulting in a total of 68 panic disorder patients and 20 healthy subjects available for study. In particular, the relationship between yohimbine's ability to produce panic attacks meeting the *DSM-III* criteria and its biochemical and cardiovascular actions was investigated.

#### **METHOD**

Sixty-eight patients gave voluntary written informed consent for their participation in the study. Fifty-eight met the DSM-III criteria for agoraphobia with panic attacks, and 10 met the criteria for panic disorder. The mean $\pm SD$  age of the 49 women was  $40\pm1$  years, and for the 19 men it was  $38\pm9$  years. All patients were outpatients and had been drug free a minimum of 3 weeks before the first yohimbine test session.

Twenty healthy subjects were determined to be free of mental disorder and to have no first-degree relatives with histories of mental illness. None of the healthy subjects reported taking any psychoactive medication for the 4 weeks before the first yohimbine test session. The mean age of the 11 women was  $43\pm7$  years, and for the nine men it was  $34\pm8$  years.

Each patient and healthy subject participated in two

test sessions. During the first test session 57 patients and 17 healthy subjects received four placebo yohimbine capsules, and during the second test session they received four capsules containing 5 mg of yohimbine each. The rest of the patients and healthy subjects received the opposite sequence. Responses to yohimbine were not related to the order in which it was given. The interval between sessions was usually 7 days.

Blood samples for determination of plasma free MHPG and cortisol levels were obtained 15 and 0.5 minutes before the yohimbine or placebo dose; 30, 60, and 90 minutes after the dose for cortisol measurement; and at 120, 180, and 240 minutes for both cortisol and MHPG measurement. Sitting and standing blood pressure and pulse rates were measured 15 minutes before and 60, 90, 120, 180, and 240 minutes after the dose.

Behavioral ratings were administered 15 minutes before and 60, 90, 120, 180, and 240 minutes after the yohimbine or placebo dose. A visual analogue scale was used to evaluate the change in anxious feelings. The scale was scored by measuring the distance in millimeters from the left-hand side of a 100-millimeter line to a perpendicular mark made by the subject at the point corresponding to his or her anxiety state at the time. Therefore, the score could range from 0 (not at all) to 100 (most ever).

Each patient was assessed by a research psychiatrist blind to medication state to determine whether he or she had had a panic attack during each test session. This determination was based on direct clinical observation and the patient's self-report. Two criteria had to be satisfied: 1) after drug administration there had to be a crescendo increase in severe subjective anxiety, reflected by a rise of at least 25 mm on the anxiety rating scale and an increase in the severity of four or more *DSM-III* panic attack symptoms, and 2) the patient must have reported that the anxiety state experienced was similar to a naturally occurring panic attack. A healthy subject was considered to have had a panic attack if the first criterion was satisfied.

Assay preparation and quantification of the samples for MHPG analysis was carried out as previously described (10, 11) (intra- and interassay coefficients of variation were 6% and 11%, respectively). Plasma cortisol concentrations were measured with a radio-immunoassay kit supplied by Clinical Assays (intra- and interassay coefficients of variation were 3% and 5%, respectively).

Analysis of variance (ANOVA) with repeated measures including baseline data allowed assessment of the statistical significance of the main effects of group (patients experiencing panic versus patients not experiencing panic versus healthy subjects), drug (placebo versus yohimbine), and time of measurement (the time points sampled). The significant interactions with group were further evaluated with paired and non-paired t tests to assess how and when the different groups differed in their responses to yohimbine.

Pearson correlations were calculated to assess the

relationship among behavioral, biochemical, and cardiovascular responses to yohimbine, reflected in net peak values (peak change after yohimbine minus peak change after placebo). Results were considered significant when they met the criterion of p<.05 with a two-tailed test. Comparisons were made with mean values, and standard deviations were used to indicate variance.

## **RESULTS**

# Behavioral Effects of Yohimbine

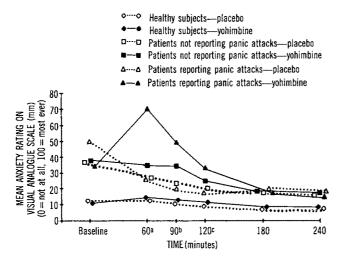
Yohimbine produced panic attacks in 37 (54%) of the 68 panic disorder patients and only one (5%) of the 20 healthy subjects (p<.001, Fisher exact test). No panic attacks occurred after placebo administration in the healthy subjects or the patients reporting panic attacks after taking yohimbine. Age and sex did not differ between the patients who had panic attacks and those who did not.

In the healthy subjects, a significant Drug by Time interaction on the ANOVA for the visual analogue rating of anxiety was not identified, and there was no significant difference between the yohimbine- and placebo-induced changes from baseline at any time point. In the total group of panic disorder patients, a significant Drug by Time interaction was found for the anxiety ratings (F=28.7, df=5, 330, p<.001). At each time point after placebo administration the mean anxiety rating was significantly lower than at baseline, and 60 minutes after yohimbine administration it was significantly higher than baseline (change=18±4 mm; t=7.4, df=67.0, p<.001). The difference between yohimbine and placebo in the increase in anxiety rating from baseline was significant for each of the first four time points after vohimbine administration.

The greater effect of yohimbine on the ratings of anxiety was almost totally accounted for by the patients who reported yohimbine-induced panic attacks. The ANOVA comparing the patients who did not experience panic attacks to the healthy subjects revealed a nonsignificant Group by Drug by Time interaction, and at no time point was there a significant difference between groups in the difference between the yohimbine- and placebo-induced changes in anxiety ratings. In contrast, a significant Group by Drug by Time interaction was seen in the comparison of the patients reporting panic attacks and the healthy subjects (F=18.0, df=5, 275, p<.001), and at 60, 90, and 120 minutes the yohimbine-placebo difference was significantly greater in these patients (figure 1).

The total group of patients had a significantly higher baseline rating of anxiety than the healthy subjects. However, there was no baseline difference in anxiety ratings between the patients who reported yohimbine-induced panic attacks and those who did not. In addition, there was no correlation between baseline anxiety and the anxiogenic effects of yohimbine in either of the patient groups or the healthy subjects.

FIGURE 1. Effects of Yohimbine and Placebo on Anxiety Self-Ratings of Healthy Subjects (N=20) and Patients With Panic Attacks Who Did (N=37) or Did Not (N=31) Report Panic Attacks After Receiving Yohimbine



<sup>a</sup>Mean change from baseline after yohimbine administration significantly greater in patients reporting panic attacks than in patients not reporting attacks (t=5.8, df=65, p<.001) or in healthy subjects (t=7.1, df=46.1, p<.001). Mean difference between yohimbine-and placebo-induced changes from baseline significantly greater for patients reporting panic attacks than for patients not reporting attacks (t=6.0, df=65, p<.001) or for healthy subjects (t=8.6, df=51.8, p<.001).

bMean change from baseline after yohimbine administration significantly greater in patients reporting panic attacks than in patients not reporting attacks (t=2.3, df=66, p<.05) or in healthy subjects (t=2.2, df=47.9, p<.05). Mean difference between yohimbine- and placebo-induced changes from baseline significantly greater for patients reporting panic attacks than for patients not reporting attacks (t=4.5, df=66, p<.001) or for healthy subjects (t=5.9, df=54.8, p<.001).

<sup>c</sup>Mean difference between yohimbine- and placebo-induced changes from baseline significantly greater for patients reporting panic attacks than for patients not reporting attacks (t=3.6, df=66, p<.001) or for healthy subjects (t=3.8, df=54.4, p<.001).

#### Yohimbine-Induced Biochemical Changes

Plasma MHPG. The ANOVA examining the effects of yohimbine on plasma MHPG levels in the healthy subjects revealed a significant Drug by Time interaction (F=15.1, df=3, 57, p<.001). This was reflected in significant differences between the yohimbine- and placebo-induced increases in MHPG at 120, 180, and 240 minutes. In the patients there was also a significant Drug by Time interaction for plasma MHPG (F=56.5, df=3, 183, p<.001) and significant yohimbine-placebo differences at 120, 180, and 240 minutes. The ANOVA comparing the effects of yohimbine on plasma MHPG levels in the total group of patients and the healthy subjects revealed a nonsignificant Group by Drug by Time interaction, and at no time point was there a significant difference between the two groups in the difference between yohimbine and placebo effects.

The patients who reported yohimbine-induced panic attacks had greater increases in plasma MHPG levels after taking yohimbine than the healthy subjects or the

patients who did not experience panic attacks. Significant Group by Drug by Time interactions were observed in the comparison of the patients who experienced panic attacks to the patients who did not (F=7.2, df=3, 180, p<.001) or to the healthy subjects (F=3.3, df=3, 155, p<.05). There were no significant differences in the changes in plasma free MHPG levels from baseline after placebo administration between the patients who experienced panic attacks and the patients who did not or the healthy subjects. In contrast, significant differences in the yohimbine-placebo differences were identified between the patients who experienced panic attacks and the patients who did not and the healthy subjects at 120, 180, and 240 minutes (table 1). The distribution of the net peak changes in MHPG levels is illustrated in figure 2.

There were no significant differences in baseline levels of plasma MHPG between the total patient group and the healthy subjects or between the patients who did and did not experience yohimbine-induced panic attacks. There was a significantly higher baseline MHPG level in the patients who experienced panic attacks than in the healthy subjects (3.8±0.8 versus  $3.3\pm0.8$  ng/ml; t=2.3, df=52, p<.05). In addition, there was a significant positive correlation between baseline plasma MHPG level and the net peak yohimbine-induced change in MHPG level in the total group of patients (r=.57, df=66, p<.001) and a trend toward significance in the healthy subjects (r=.40, df=18, p=.08). Baseline MHPG levels did not significantly correlate to baseline ratings of anxiety or yohimbine-induced changes in MHPG levels. There was a significant positive correlation between the net peak changes in the anxiety rating and the plasma free MHPG level (r=.37, df=66, p<.003) in the patients but not in the healthy subjects (r=.03, df=18, p=.92).

Cortisol. In the healthy subjects yohimbine did not significantly increase plasma cortisol levels, as reflected in a nonsignificant Drug by Time interaction (F=1.7, df=5, 135, p=.16), and at no time point was the yohimbine-placebo difference significantly greater than at baseline. In contrast, in the 52 patients for whom cortisol was measured there was a significant Drug by Time interaction (F=14.2, df=5, 225, p<.001), and there were significant differences between the yohimbine- and placebo-induced increases from baseline 60, 90, and 120 minutes after the dose.

The yohimbine-induced changes in cortisol level were somewhat greater in the patients who experienced yohimbine-induced panic attacks than in those who did not. The ANOVA comparing the two patient groups revealed a nonsignificant Group by Drug by Time interaction. However, only the patients who experienced panic attacks had significant increases in cortisol level from baseline after yohimbine administration. These increases occurred at 60 and 90 minutes and were significantly greater than the changes in cortisol level at 60 and 90 minutes in the patients who did not report panic attacks (figure 3).

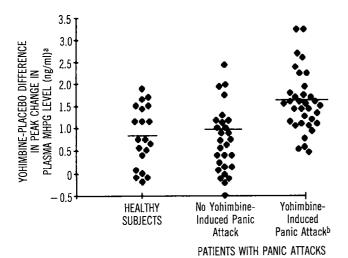
There was a significantly higher baseline cortisol

TABLE 1. Effects of Yohimbine and Placebo on Plasma Free MHPG Levels of Healthy Subjects and Panic Disorder Patients Who Did or Did Not Report Panic Attacks After Receiving Yohimbine

			M	IHPG Le	evel (ng/ml)					
				(	Change From Baseline					
	Basel	ine	120 mi	nutes	180 mi	nutes	240 mi	nutes		
Group and Drug	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Healthy subjects (N=20)										
Placebo	3.5	0.9	0.2	0.4	0.1	0.3	0.2	0.6		
Yohimbine	3.2	0.7	1.0	0.6	1.0	0.7	0.8	0.6		
Yohimbine-placebo difference <sup>a</sup>	_	_	0.9	0.7	0.9	0.7	0.7	1.0		
Patients not reporting panic attacks after vohimbine (N=31)										
Placebo	3.5	0.9	0.3	0.3	0.2	0.4	0.1	0.4		
Yohimbine	3.6	1.1	0.9	0.7	1.0	0.8	0.7	0.8		
Yohimbine-placebo difference <sup>a</sup>	_	_	0.6	0.7	0.8	0.8	0.5	0.8		
Patients reporting panic attacks after vohimbine (N=37)										
Placebo	3.8	0.8	0.3	0.4	0.1	0.6	0.3	0.5		
Yohimbine	3.8	0.8	1.7 <sup>b</sup>	0.8	1.6°	0.8	1.4 <sup>d</sup>	0.9		
Yohimbine-placebo difference <sup>a</sup>	_	_	1.5 <sup>e</sup>	0.7	1.5 <sup>f</sup>	0.9	1.2 <sup>g</sup>	0.8		

<sup>&</sup>lt;sup>a</sup>Yohimbine-placebo difference=(level after yohimbine minus baseline level) minus (level after placebo minus baseline level).

FIGURE 2. Difference Between Yohimbine- and Placebo-Induced Changes in Plasma MHPG Levels of Healthy Subjects (N=20) and Patients With Panic Attacks Who Did (N=37) and Did Not (N=31) Report Panic Attacks After Receiving Yohimbine



<sup>a</sup>Yohimbine-placebo difference=(peak level after yohimbine minus baseline level) minus (peak level after placebo minus baseline level. <sup>b</sup>Mean difference significantly greater than that for patients not reporting panic attacks (t=4.6, df=60, p<.001) or for healthy subjects (t=3.9, df=52, p<.001).

level in the total patient group than in the healthy subjects (11.6 $\pm$ 4.6 versus 9.2 $\pm$ 2.9; t=2.0, df=66, p<.05) but no difference between the patients reporting panic attacks and the healthy subjects or the

patients who did not report panic attacks. There was no correlation between baseline cortisol level and yohimbine-induced changes in cortisol level. A significant positive correlation was seen between the peak changes in anxiety and cortisol level in the patients (r=.32, df=50, p<.05) but not in the healthy subjects (r=.26, df=18, p=.35). There was no correlation between peak change in plasma MHPG level and baseline or peak change in cortisol level in either the healthy subjects or patients.

## Cardiovascular Effects of Yohimbine

Significant Drug by Time interactions for sitting systolic (F=2.4, df=5, 185, p<.05), standing systolic (F=2.8, df=5, 190, p<.05), and standing diastolic (F=3.8, df=5, 185, p<.01) blood pressure were observed in the healthy subjects. There were significant yohimbine-placebo differences (5–7 mm Hg) in the increases from baseline in sitting systolic blood pressure 60, 120, and 180 minutes after the dose; in standing systolic blood pressure 90, 120, 180, and 240 minutes after the dose.

Yohimbine had greater effects on blood pressure in the patients than in the healthy subjects. Significant Drug by Time interactions were found in the patients for sitting systolic blood pressure (F=19.1, df=5, 335, p<.001), standing systolic blood pressure (F=16.0, df=5, 330, p<.001), sitting diastolic blood pressure (F=4.9, df=5, 335, p<.001), standing diastolic blood

bSignificantly greater than change in patients not reporting panic attacks (t=4.3, df=60, p<.001) or in healthy subjects (t=3.7, df=52, p<.001).

cSignificantly greater than change in patients not reporting panic attacks (t=2.8, df=60, p<.01) or in healthy subjects (t=2.6, df=52, p<.01).

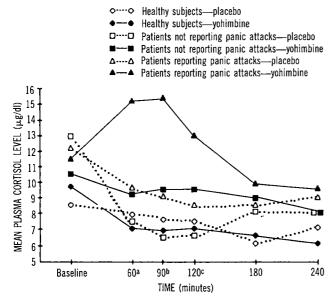
dSignificantly greater than change in patients not reporting panic attacks (t=3.4, df=60, p<.01) or in healthy subjects (t=2.7, df=52, p<.01).

eSignificantly greater than difference for patients not reporting panic attacks (t=4.8, df=60, p<.001) or for healthy subjects (t=3.3, df=52, p<.001).

fsignificantly greater than difference for patients not reporting panic attacks (t=3.0, df=60, p<.01) or for healthy subjects (t=2.4, df=52, p<.05).

geometric greater than difference for patients not reporting panic attacks (t=3.0, df=60, p<.01) or for healthy subjects (t=2.1, df=52, p<.05).

FIGURE 3. Effects of Yohimbine and Placebo on Plasma Cortisol Levels of Healthy Subjects (N=20) and Patients With Panic Attacks Who Did (N=29) or Did Not (N=23) Report Panic Attacks After Receiving Yohimbine



<sup>a</sup>Mean change from baseline after yohimbine administration significantly greater in patients reporting panic attacks than in patients not reporting attacks (t=2.7, df=46, p<.01) and healthy subjects (t=4.8, df=38.2, p<.001). Mean difference between yohimbine-and placebo-induced changes from baseline significantly different between patients reporting panic attacks and healthy subjects (t=5.1, df=41.8, p<.001) and between patients not reporting panic attacks and healthy subjects (t=3.1, df=33, p<.01).

panic attacks and healthy subjects (t=3.1, df=33, p<.01). <sup>b</sup>Mean change from baseline after yohimbine administration significantly greater in patients reporting panic attacks than in patients not reporting attacks (t=2.5, df=46, p<.05) and healthy subjects (t=4.8, df=40.4, p<.001). Mean difference between yohimbine and placebo-induced changes from baseline significantly different between patients reporting panic attacks and healthy subjects (t=5.5, df=41.7, p<.001) and between patients not reporting panic attacks and healthy subjects (t=3.4, df=27.1, p<.01).

<sup>c</sup>Mean change from baseline after yohimbine administration significantly greater in patients reporting panic attacks than in healthy subjects (t=2.6, df=45, p<.01). Mean difference between yohimbine- and placebo-induced changes from baseline significantly different between patients reporting panic attacks and healthy subjects (t=3.2, df=45, p<.01) and between patients not reporting panic attacks and healthy subjects (t=2.4, df=28.8, p<.05).

pressure (F=4.0, df=5, 330, p<.01), sitting heart rate (F=2.6, df=5, 335, p<.05), and standing heart rate (F=2.3, df=5, 330, p<.05). There were significant yohimbine-placebo differences (6–14 mm Hg) in the increases from baseline in sitting and standing systolic blood pressure at all five time points after the dose. There were also significant yohimbine-placebo differences in the increases from baseline in sitting and standing diastolic blood pressure at 60 minutes (4 mm Hg) and in sitting and standing heart rate at 60, 180, and 240 minutes (3–5 beats/minute).

Patients who reported yohimbine-induced panic attacks had slightly greater changes in blood pressure than patients who did not. Although there was not a significant Group by Drug by Time interaction and at

no time point were the yohimbine-placebo differences significantly different between the two patient groups, the net peak changes after yohimbine administration in sitting and standing systolic blood pressure were significantly greater than those of healthy subjects only in patients who reported panic attacks (figure 4).

The patients who experienced yohimbine-induced panic attacks appeared to have a greater increase in heart rate than the patients who did not. Only the patients experiencing panic attacks had significant yohimbine-placebo differences in the peak increases in heart rate: sitting heart rate at 180 minutes ( $7\pm3$  beats/minute; t=2.8, df=36, p<.01) and standing heart rate at 60 minutes ( $6\pm2$  beats/minute; t=2.5, df=35, p<.05) and 180 minutes ( $6\pm2$  beats/minute; t=2.4, df=36, p<.05). The peak changes in sitting and standing heart rate in the healthy subjects and patients are illustrated in figure 5.

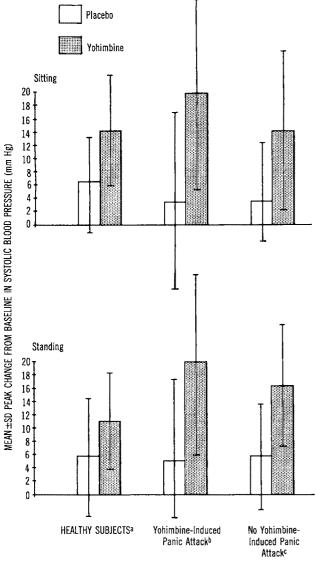
The patients reporting yohimbine-induced panic attacks had a significantly higher baseline heart rate than the healthy subjects, both for sitting (80±1 versus 74±2 beats/minute; t=2.4, df=55, p<.05) and standing (85±2 versus 78±2 beats/minute; t=2.5, df=55, p<.05). There was no correlation between baseline blood pressure or heart rate and the yohimbine-induced changes in these variables. There was also no correlation between the yohimbine-induced changes in anxiety, MHPG level, or cortisol level and changes in blood pressure or heart rate.

## **DISCUSSION**

The findings of the present investigation using yohimbine as an anxiogenic probe support the hypothesis that abnormally high noradrenergic activity may be critically involved in the neurobiological mechanism that produces panic attacks in at least some panic disorder patients. In this study oral yohimbine produced panic attacks in approximately 54% of the patients, and the symptoms reported were similar to those of their naturally occurring panic attacks. In addition, the patients who experienced yohimbineinduced panic attacks had greater increases in plasma MHPG, cortisol, systolic blood pressure, and heart rate than healthy subjects. The specificity of these findings is supported by the findings in recent studies that yohimbine does not produce similar effects in patients with schizophrenia, major depression, generalized anxiety disorder, or obsessive-compulsive disorder (12–14).

There is considerable preclinical evidence (2, 15, 16) that the anxiogenic properties of yohimbine are mediated through its ability to increase presynaptic noradrenergic activity by antagonizing the  $\alpha_2$ -adrenergic autoreceptor. The abnormally high presynaptic neuronal activity in our patients who experienced yohimbine-induced panic attacks, as reflected by yohimbine's ability to produce anxiety and raise plasma MHPG levels, may be due to dysfunction at a number of

FIGURE 4. Effects of Yohimbine and Placebo on Sitting and Standing Systolic Blood Pressure of Healthy Subjects (N=20) and Patients With Panic Attacks Who Did (N=37) or Did Not (N=31) Report Panic Attacks After Receiving Yohimbine



PATIENTS WITH PANIC ATTACKS

<sup>a</sup>Mean peak change from baseline significantly greater after yohimbine than after placebo for sitting (t=2.9, df=19, p<.01) and standing (t=2.2, df=18, p<.05).

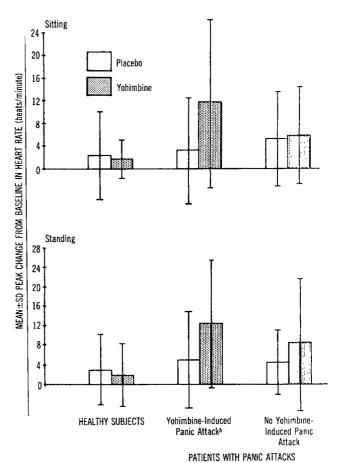
<sup>b</sup>Mean peak change from baseline significantly greater after yohimbine than after placebo for sitting (t=6.0, df=36, p<.001) and standing (t=5.8, df=36, p<.001). Mean difference between peak yohimbine- and placebo-induced changes from baseline significantly greater than difference in healthy subjects for sitting (t=2.0,df=55, p<.05) and standing (t=2.3, df=54, p<.05).

<sup>c</sup>Mean peak change from baseline significantly greater after yohimbine than after placebo for sitting (t=4.8, df=30, p<.001) and

standing (t=6.0, df=30, p<.001).

different sites. For example, as reviewed elsewhere (3), noradrenergic neurons, such as those of the locus coeruleus, are regulated not only by the  $\alpha_2$ -adrenergic autoreceptor but also by other neuronal systems, including benzodiazepine receptors, endogenous opiates,

FIGURE 5. Effects of Yohimbine and Placebo on Sitting and Standing Heart Rates of Healthy Subjects (N=20) and Patients With Panic Attacks Who Did (N=37) or Did Not (N=31) Report Panic Attacks After Receiving Yohimbine



<sup>a</sup>Mean peak change from baseline significantly greater after yohimbine than after placebo for sitting (t=3.2, df=36, p<.01) and standing (t=2.8, df=36, p<.05). Mean difference between peak yohimbine- and placebo-induced changes from baseline significantly greater than difference in healthy subjects for sitting (t=2.9, df=54.2, p<.01) and standing (t=2.4, df=52.4, p<.05) and in

patients not reporting attacks for sitting (t=2.4, df=63.6, p<.05).

serotonin, acetylcholine, γ-aminobutyric acid, epinephrine, corticotropin-releasing hormone, and substance P (3). The mechanism responsible for the excessive anxiety produced by yohimbine in the patients may also depend on the increased stimulation of  $\alpha_1$ - and  $\beta$ adrenergic postsynaptic receptors by norepinephrine in a variety of brain regions and the peripheral nervous system. It is possible that the direct blockade of the postsynaptic  $\alpha_2$  receptor by yohimbine also relates to yohimbine's anxiogenic properties (2-4).

The effects of yohimbine on plasma cortisol level, blood pressure, and heart rate do not provide a specific index of noradrenergic function. The ability of yohimbine to increase cortisol level and blood pressure may be due to either pre- or postsynaptic effects or the balance between the two. There is a considerable body of preclinical data indicating that norepinephrine has stimulatory effects on blood pressure and cortisol secretion. On the other hand, there is also evidence that postsynaptic  $\alpha_2$  receptors have inhibitory actions on blood pressure regulation and cortisol secretion (17–22). The ability of yohimbine to produce greater increases in blood pressure and cortisol in the panic disorder patients may be due to a yohimbine-induced increase in norepinephrine release, a subsensitivity of postsynaptic  $\alpha_2$  receptors, or the abnormal regulation of these receptors by other neuronal systems. The greater heart rate elevations produced by yohimbine in the patients who experienced yohimbine-induced panic attacks may also relate to dysfunction of either pre- or postsynaptic  $\alpha_2$ -adrenergic receptors.

The greater increases in blood pressure and heart rate after yohimbine administration in the patients reporting yohimbine-induced panic attacks are consistent with the neuroanatomical and neurophysiological evidence indicating a functional interaction between the activity of noradrenergic neurons in the spinal cord and medulla involved in cardiovascular regulation and forebrain neurons involved in both cardiovascular function and the behavioral expression of anxiety and fear (3–7).

Considered together, the findings of the present investigation are consistent with a conceptual model of panic anxiety which suggests that spontaneous and phobic-stimulus-induced panic attacks may result from dysfunction of the α2-adrenergic autoreceptor and other neuronal inputs. Such dysfunction might result in improper regulation of the normal fluctuations in noradrenergic neuronal activity that occur in response to mild, nonnoxious stimuli or of the increased norepinephrine neuronal activity and norepinephrine release that occur in response to stress (3, 5, 23). Under normal conditions, increased norepinephrine release would act as feedback to decrease neuronal activity by stimulating the inhibitory  $\alpha_2$ -adrenergic autoreceptor. However, this mechanism could be impaired in patients in whom the activity of this receptor is abnormally low, thereby producing a prolonged state of noradrenergic hyperactivity and panic anxiety. The therapeutic mechanism of antipanic treatment may relate to an ability to attenuate the surge of noradrenergic activity associated with panic anxiety by reducing presynaptic noradrenergic activity and/or by downregulating postsynaptic β-adrenergic receptors (24, 25).

## REFERENCES

- Redmond DE Jr: New and old evidence for the involvement of a brain norepinephrine system in anxiety, in The Phenomenology and Treatment of Anxiety. Edited by Fann WE. New York, Spectrum Publications, 1979
- 2. Charney DS, Heninger GR, Breier A: Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 1984; 41:751–763
- Foote SL, Bloom FE, Aston-Jones G: Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. Physiol Rev 1983; 63:844–914
- 4. Unnerstall JR, Kopajtic TA, Kuhar MJ: Distribution of  $\alpha_2$

- agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res Rev 1984; 7:69–101
- 5. Glavin GB: Stress and brain noradrenaline: a review. Neurosci Biobehav Rev 1985; 9:233–243
- Felten DL, Sladek JR Jr: Monoamine distribution in primate brain, V: monoaminergic nuclei: anatomy, pathways and local organization. Brain Res Bull 1983; 10:171–284
- 7. Sawchenko PE, Swanson LW: Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. Science 1981; 214:685–687
- Cameron OG, Smith CB, Hollingsworth PJ, et al: Platelet α<sub>2</sub>-adrenergic receptor binding and plasma catecholamines: before and during imipramine treatment in patients with panic anxiety. Arch Gen Psychiatry 1984; 41:1144–1148
- Charney DS, Woods SW, Goodman WK, et al: Abnormal regulation of noradrenergic function in panic disorders. Neurosci Abstracts 1986; 12:1162
- Dekirmenjian H, Maas JW: MHPG in plasma. Clin Chim Acta 1974; 52:203–208
- 11. Maas JW, Hattox SE, Roth RH: The determination of a brain arteriovenous difference for 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG). Brain Res 1976; 118:167–174
- Glazer WM, Charney DS, Heninger GR: Norepinephrine, tardive dyskinesia, and schizophrenia, in CME Syllabus and Scientific Proceedings in Summary Form, 139th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1986, p 150
- 13. Charney DS, Heninger GR, Price LH, et al: Major depression and panic disorder: diagnostic and neurobiological relationships. Psychopharmacol Bull 1986; 22:503–511
- 14. Goodman WK, Price LH, Rasmussen SA, et al: Evidence for abnormal serotonergic function in obsessive compulsive disorder. Neurosci Abstracts 1986; 12:1161
- Starke K, Borowski E, Endo T: Preferential blockade of presynaptic α-adrenoceptors by yohimbine. Eur J Pharmacol 1975; 34:385–388
- Cedarbaum JM, Aghajanian GK: Catecholamine receptors on locus coeruleus neurons: pharmacological characterization. Eur J Pharmacol 1977; 44:375–385
- 17. Rudolph CD, Kaplan SL, Ganong WF: Sites at which clonidine acts to affect blood pressure and the secretion of renin, growth hormone and ACTH. Neuroendocrinology 1980; 31:121–128
- Reid IA, Ahn JN, Trinh T, et al: Mechanism of suppression of vasopressin and adrenocorticotropic hormone secretion by clonidine in anesthetized dogs. J Pharmacol Exp Ther 1984; 229: 1–8
- 19. Shimizu K: Effect of  $\alpha_1$  and  $\alpha_2$ -adrenoceptor agonists and antagonists on ACTH secretion in intact and in hypothalamic deafferentated rats. Jpn J Pharmacol 1984; 36:23–33
- Kobinger W: α-Adrenoceptors in cardiovascular regulation, in Norepinephrine. Edited by Ziegler MG, Lake CR. Baltimore, Williams & Wilkins, 1984
- Tung CS, Onuora CO, Robertson D, et al: Hypertensive effect
  of yohimbine following selective injection into the nucleus
  tractus solitarii of normotensive rats. Brain Res 1983; 277:193

  195
- Bousquet P, Schwartz J: Commentary: alpha-adrenergic drugs: pharmacological tools for the study of the central vasomotor control. Biochem Pharmacol 1983; 32:1459–1465
- Foote SL, Aston-Jones G, Bloom FE: Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc Natl Acad Sci USA 1980; 77:3033–3037
- Charney DS, Heninger GR: Noradrenergic function and the mechanism of action of antianxiety treatment, I: the effect of long-term alprazolam treatment. Arch Gen Psychiatry 1985; 42:458-467
- Charney DS, Heninger GR: Noradrenergic function and the mechanism of action of antianxiety treatment, II: the effect of long-term imipramine treatment. Arch Gen Psychiatry 1985; 42:473-481

# Effect of Bromocriptine on Affect and Libido in Hyperprolactinemia

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Six women with primary hyperprolactinemia (mean prolactin level, 50 ng/ml) were matched with six normal women on eight factors influencing life style. Observers blind to endocrine status followed the subjects weekly for 10 weeks. Patients took bromocriptine, 2.5 mg twice daily, or placebo in a randomized double-blind sequence with crossover at 5 weeks. The mean Hamilton score for the patients was compatible with mild depression and higher than that for normal subjects during placebo but not during bromocriptine treatment. Libido was similar in both groups during placebo and bromocriptine. The mean number of orgasms reported per day was lower in patients than in normal subjects during both treatment conditions, although one patient reported orgasms during drug treatment only. Hyperprolactinemia in women may be associated with mild depression and a decrease in orgasmic

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Hyperprolactinemia, a common disorder in young women, may cause symptoms of galactorrhea, menstrual irregularity, or infertility. A subset of these patients also have a pituitary tumor. Recent studies (1–3) document that tumor progression is infrequent and that prolonged clinical stability or gradual improvement is the rule. Thus, ablative therapy of the adenoma is rarely indicated, and treatment should be aimed at controlling symptoms. Several workers (4, 5) have suggested that hyperprolactinemic individuals have psychological disturbances which, if causally related to the hyperprolactinemia, could be indications for pro-

lactin-lowering therapy with dopamine agonists such as bromocriptine. However, the choice of healthy hospital employees as a control group for hospitalized hyperprolactinemic women (4) was a poor one because of the psychological stress related to hospitalization and the inability to conduct a blind structured interview.

Loss of libido is generally considered a cardinal manifestation of hyperprolactinemia in women, but this is largely based on subjective determinations made by biased observers. One previous study (6) assessed sexuality by questionnaires administered to treated and untreated hyperprolactinemic women and unmatched control subjects. Thus, several questions remain. Is decreased libido a consistent finding in hyperprolactinemic women when such women are compared to normal subjects matched for life style? If so, is it a consequence of central actions of prolactin on sexual behavior? Is it secondary to associated changes in mental status or gonadal function? Or is it an epiphenomenon of central neurotransmitter alterations either causing or caused by the hyperprolactinemia? The study by Adams et al. (7) illustrates the importance of evaluating female-initiated sexual activity in studies of female sexuality and libido. To examine the possible effect of hyperprolactinemia on libido and affect, we studied sexuality in parallel with assessments of mood, affect, and hormone levels. Observers were blind to the endocrine status of the subjects. Hyperprolactinemic women were studied during blind placebo and bromocriptine treatment conditions and compared with concomitantly followed, matched normoprolactinemic control subjects.

#### **METHOD**

Women with primary hyperprolactinemia (mean baseline prolactin level >3 SD above the normal mean) living in the greater Washington, D.C., area were invited to participate in this protocol. Each recruited patient was then matched with a normal control subject drawn from a pool of more than 500 women who responded, by completing a questionnaire, to a call for volunteers for a study of relationships between hormone levels and mood. Normal subjects, but not

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patients, were remunerated for their participation. All subjects gave written informed consent. The protocol was approved by the National Institute of Child Health and Human Development Clinical Research Committee.

All subjects were matched as closely as possible on eight factors influencing life style. These factors were weighted in descending order: race, marital status and duration, number of children at home, age, contraceptive method, religion, and employment status. No subject used oral contraceptives. All normal subjects reported regular menstrual cycles.

We obtained a complete medical history from each patient and normal subject. All subjects were given a physical examination and a short form of the MMPI to assess baseline status. Patients were then randomly assigned to placebo or bromocriptine (2.5 mg b.i.d.) for 5 weeks and crossed over for the second 5 weeks. Normal subjects received no medication.

Subjective ratings of affect were assessed daily by means of a questionnaire that scores sleep, sadness, anxiety, fatigue, and energy. Each subject kept daily inventories of sexual activity, using a form modified from Adams et al. (7), for the duration of the study. Each week for 10 weeks objective determinations of mood and affect were made by psychiatrists (B.L.P. and J.A.H.) who were blind to the endocrine status of the subjects. Objective measures were obtained by means of a structured interview that included a mental status examination and questions (Hamilton Rating Scale for Depression, 24 items) to evaluate mood (depression, anxiety, hostility, irritability), neurovegetative status (sleep, appetite, libido, memory-concentration, energy), and somatic symptoms (8, 9). The Profile on Mood States (POMS) (10) was administered weekly for the subjective component.

Before each interview, 30 ml of blood were drawn for measurement of prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, testosterone, dihydrotestosterone, testosterone-estradiol-binding globulin, cortisol, and dehydroepiandrosterone sulfate (DHA-S). Serum was separated and stored frozen until all samples were collected. All samples for each patient and matched normal subject were run in one assay.

Prolactin (11), LH, and FSH were measured by double antibody radioimmunoassays with reagents provided by the National Hormone and Pituitary Program of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and a commercial prolactin standard (65A6LB1, Cambridge Medical Diagnostics, Billerica, Mass.). Serum estradiol, testosterone, and dihydrotestosterone were measured by radioimmunoassay after diethyl ether extraction and celite chromatography. Progesterone was measured by radioimmunoassay after hexane extraction. Testosterone-estradiol-binding globulin was determined by the method of Nisula and Dunn (12). Cortisol and DHA-S were measured by radioimmunoassay. The within- and between-assay coefficients of variation, respectively,

were as follows: prolactin, 3.0% and 12.4%; LH, 8.4% and 17.5%; FSH, 8.1% and 16.2%; estradiol, 5.2% and 10.4%; testosterone, 10.0% and 14.3%; dihydrotestosterone, 13.3% and 24.7%; progesterone, 7.5% and 12.8%; cortisol, 5.8% and 10.1%; and DHA-S, 6.5% and 13.0%.

Comparisons between patients and control subjects (group effect) were made by unpaired t tests of each measure averaged for the last 4 weeks of each 5-week time period: placebo (block 1) or bromocriptine (block 2) for the patients and the corresponding time period for the normal subjects (also referred to as blocks 1 and 2). Drug effect was evaluated by two-sided t tests of the difference between each factor during block 1 and block 2 for patients compared to the difference for the normal subjects. The limit of significance was .05 for each test. All values are reported as mean ±SD.

#### **RESULTS**

The hyperprolactinemic subjects had had symptoms of amenorrhea and/or galactorrhea for 7.3±3.0 years (range, 3-10) and documented prolactin elevation for  $4.6\pm1.8$  years (range, 2–7.5). Five of the six subjects had had CAT scans of the sella within 2 years of study. All abnormalities documented were confined to the sella. The sixth patient did not have a CAT scan but did have a normal skull X-ray (Hardy grade 0) within 2 years of this study. One patient was withdrawn from bromocriptine for 6 weeks before the protocol began. Two other subjects had taken bromocriptine for ovulation induction more than 18 months before study. None of the patients had undergone transsphenoidal surgery or pituitary irradiation. Two patients had regular menses; the other four were amenorrheic. The means of two or three random prolactin levels, obtained in all subjects before the study began, were  $49.8\pm17.4$  ng/ml for the patients and  $13.0\pm7.1$  for the normal subjects (t=4.8, df=10, p<.001).

Four of the six matched pairs were white and two were black. Three subjects in each cohort were married, two were single, and one was married and recently separated. Two subjects in each cohort had young children living at home; they ranged in age from 9 months to 9 years. The age range of the patients was 21–37 years; the age range of the normal subjects was 21–36 years. The patients and the normal subjects reported similar tobacco and alcohol use and were of similar socioeconomic status.

Five patients and five normal subjects reported previous use of oral contraceptives for up to 3 years, but all 10 had stopped taking oral contraceptives more than 3 years before study. Subject 5 in each cohort reported no previous use of oral contraceptives. All patients and normal subjects were clinically and chemically euthyroid. One normal subject was taking L-thyroxine because of a history of goiter. No other subjects took prescription medications during the study.

TABLE 1. Total Hamilton Depression Scores, Measures of Libido, and Hormonal Data for Hyperprolactinemic Women Given Placebo and **Bromocriptine and for Normal Women** 

	Hamilton Score Net Events/Day <sup>a</sup>		Orgasms/Day		Prolactin (ng/ml)		Estradiol (pg/ml)		Progesterone (ng.ml)			
Subjects	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients (N=6)												
Block 1 (placebo)	9.1 <sup>b</sup>	4.6	0.31	0.17	0.008c	0.019	44.6 <sup>d</sup>	20.1	40.3 <sup>e</sup>	.50.1	0.7 <sup>f</sup>	0.9
Block 2 (bromocriptine)	4.4 <sup>g</sup>	1.8	0.36	0.19	0.059°	0.092	$19.6^{\rm h}$	22.2	49.2	49.5	1.0 <sup>f</sup>	1.4
Normal (N=6)												
Block 1	3.9	2.4	0.58 <sup>i</sup>	0.29	0.231	0.192	7.8	2.4	113.8	45.2	4.7	2.4
Block 2	4.6	3.2	0.45 <sup>i</sup>	0.23	0.231	0.165	5.8	2.4	77.8	7.0	3.9	2.1

<sup>&</sup>lt;sup>a</sup>Number of mutually and female-initiated hetero- and autosexual events minus rejections of partner.

MMPIs were completed by five patients and six normal subjects before they entered the study, although the results were not tabulated until the study was finished. Except for the depression subscale raw scores (25.4 $\pm$ 4.6 in patients and 19.5 $\pm$ 2.7 in normal subjects; t=2.64, df=9, p<.05), the mean scores for each of the 10 subscales did not differ in the two groups. Only one patient had a score on the depression subscale in the range considered "possibly pathologic." Three patients had borderline pathologic values (T score greater than 70) on one to three subscales each (psychopathic deviate, N=2; mania, N=1; depression, N=1; schizophrenia, N=1). Three normal subjects had borderline pathologic values (T score greater than 70) on one to two subscales each (mania, N=1; psychopathic deviate, N=1; schizophrenia, N=1; social introversion, N=1).

The interobserver correlation on the Hamilton ratings was .83 for our two raters. The Hamilton total scores for 24 items were higher for the patients than for the normal subjects during block 1 (placebo) but not during block 2 (bromocriptine) (table 1). During the placebo phase, four patients had total Hamilton scores that indicated mild to moderate depression (range, 7-15), which resulted from a diffuse increase in scores across many scales; the score on only one subscale (psychomotor retardation) was significantly different between patients and normal subjects during placebo  $(.47\pm.25 \text{ versus } .17\pm.13; \text{ t}=2.70, \text{ df}=10, \text{ p}<.05) \text{ but}$ not during bromocriptine ( $.22\pm.40$  versus  $.26\pm.32$ ).

Despite the significant difference between patients and normal subjects on the depression scale of the MMPI and objective evidence of depression as determined by the observed Hamilton ratings, there was no difference between patients and normal subjects in subjective assessment of mood. Both groups gave similar responses on all subscales of the POMS during both intervals. Responses of both groups were also similar on the daily mood ratings during block 1 (placebo). Patients were significantly more anxious than normal subjects during block 2 (bromocriptine), largely because of a lower anxiety score reported by normal subjects during this block (t=3.44, df=5, p<.02).

One measure of libido (net events per day) was calculated from the number of mutually or self-initiated hetero- and autosexual events minus rejections of partner averaged per day. This measure was similar in patients and normal subjects during both blocks (table 1). Because two normal subjects did not consistently indicate the initiator of sexual activity on their inventories, their data could not be used for analysis of the female-initiated sexual activity. Neither hetero- nor autosexual events were significantly fewer in patients than in normal subjects. Patients reported significantly fewer orgasms per day than did normal subjects during both blocks (table 1). Five of six patients and one of six normal subjects reported no orgasms during block 1. One of six patients and three of six normal subjects reported masturbating.

Prolactin levels were significantly higher in patients than in normal subjects during block 1 (placebo) but not during block 2 (bromocriptine) (table 1). Estradiol levels were lower in patients than in normal subjects during placebo, and progesterone levels were lower in patients than in normal subjects during both blocks (table 1). There were no differences between patients and normal subjects during either block in levels of LH, FSH, testosterone, dihydrotestosterone, testosterone-estradiol-binding globulin, cortisol, or DHA-S.

The Hamilton scores of the patients fell significantly during bromocriptine treatment (figure 1), largely because of the normalization of the abnormal ratings seen in four patients. The drug effect on the Hamilton scores was predominantly on two subscales, depressed mood (t=3.51, df=10, p<.01) and somatic general (t=3.19, df=10, p<.02). The reduction in Hamilton ratings did not correlate with the degree of suppression of prolactin.

Although the POMS subscale scores for patients

 $b_t=2.46$ , df=10, p<.05; group effect, block 1.

t=2.83, df=10, p<.05; group effect, block 1. t=2.22, df=10, p<.05; group effect, block 2.

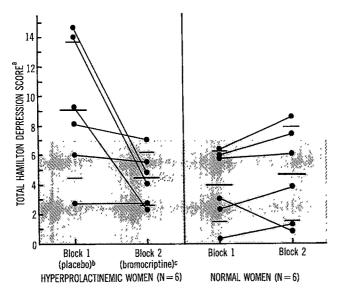
 $<sup>^{</sup>d}t=4.45$ , df=10, p<.001; group effect, block 1.

et=2.67, df=10, p<.05; group effect, block 1.

ft=3.73, df=10, p<.01; group effect, block 1. t=2.90, df=10, p<.05; group effect, block 2.

gt=2.54, df=10, p<.05; drug effect. ht=2.93, df=10, p<.05; drug effect.

FIGURE 1. Individual Total Hamilton Depression Scores for Hyperprolactinemic Woman Given Placebo and Bromocriptine and for Normal Women



<sup>a</sup>Shaded area indicates normal range. Horizontal lines indicate means and standard deviations.

bt=2.46, df=10, p<.05; group effect.

ct=2.54, df=10, p<.05; drug effect.

were indistinguishable from those of the normal subjects during both blocks, the patients' scores were significantly lower (but still within the normal range) than the normal subjects' scores on one subscale, confusion (4.44±2.50 versus 4.97±3.12 during block 1 and  $2.58\pm1.23$  versus  $5.15\pm2.83$  during block 2; drug effect, t=2.65, df=10, p<.05). No significant changes were seen in the daily mood ratings.

There was a nonsignificant increase in libido and orgasms from block 1 to block 2 for the patients (table 1). One patient reported orgasms while taking bromocriptine but not placebo, and another patient reported orgasms during both blocks. Both patients who reported orgasms were having regular menses and ovulatory levels of progesterone before and during the study. The one patient who reported orgasms during placebo had been withdrawn from bromocriptine 6 weeks before entering this study and despite elevation of prolactin (42.7 ng/ml) continued to have regular menses. The four anorgasmic subjects remained amenorrheic during the study. There was no correlation between increase in libido and either decrease in Hamilton ratings or suppression of prolactin.

Maintaining the blind status for the psychiatrists was successful. At the end of the study, they succeeded in correctly identifying the prolactin status (high or normal) of six of the 12 participants. One patient had substantial side effects of nausea and dizziness while taking bromocriptine, which were ameliorated by taking both capsules at bedtime. When the study was finished, five of six patients correctly identified the block during which they received the drug. Only one of

the six wished to continue bromocriptine after completion of the study.

#### DISCUSSION

The findings of this study confirm the tendency to mild depression previously described in women with hyperprolactinemia (4, 5). However, our patients were not more hostile or anxious by objective criteria and did not report more subjective emotional distress than the normoprolactinemic women. The observations, reflected by the Hamilton scores, made by psychiatrists blind to endocrine status were considerably more sensitive to differences in mood than the subjective information obtained on the POMS. This blind design has not been implemented in previous studies of affect in hyperprolactinemia. Thus, the reported differences in the Hamilton scores do not reflect observer bias.

Despite reporting levels of female-initiated sexual activity similar to the normal subjects' levels as well as to previously reported levels of normal women (7), the hyperprolactinemic women reported significantly fewer orgasms. This observation has not been previously reported. Thus, while the quantitative experience is similar, the quality may not be. The complaints of abnormal or decreased libido most likely connote this qualitative change. Our findings are in contrast to a previous evaluation of sexuality in hyperprolactinemic women that used a pencil-and-paper questionnaire to assess libido (6), in which measures of "sexual activity" and "interest in intercourse" were significantly reduced and no significant difference was reported in "ability to reach orgasm" or "satisfaction of intercourse."

Our patients had had a diagnosis of primary hyperprolactinemia for 2-7.5 years before they entered the study. The two who desired children had taken bromocriptine and had had healthy full-term infants. These patients and their physicians viewed their illness as a chronic but benign condition that offers little, if any, impairment to their daily life. By contrast, the patients previously described as having high levels of anxiety and hostility were either newly diagnosed or newly referred to an endocrine clinic (4, 5); they had recently had or were undergoing a complete evaluation of pituitary function, including anatomic studies. Thus, the anxiety experienced by patients referred to a subspecialty clinic and undergoing extensive evaluation may have been nurtured by their physicians and elicited on their symptom questionnaires.

The effects of bromocriptine treatment on depressed mood were significant. The four patients with objective evidence of depression (Hamilton scores greater than 7) returned to normal mood. By averaging measures obtained weekly over 4 weeks, we can control for cyclic variation in patients or in normal subjects. In a double-blind study, bromocriptine was found to be more effective than imipramine for mild endogenous depression (13). The absence of a correlation between improvement in Hamilton scores and degree of suppression of prolactin in our study suggests that the antidepressant and prolactin-lowering actions of bromocriptine may be independent.

The reporting of orgasms was a stable factor for the normal subjects, with five of the six normal subjects reporting orgasms during both blocks and the sixth during neither. One patient reported orgasms while taking bromocriptine but not placebo, suggesting an effect of treatment for that individual. The two hyperprolactinemic patients who reported orgasms were having regular menses with ovulatory levels of progesterone during both placebo and bromocriptine blocks. The lesser degree of impairment of orgasmic potential in these subjects may reflect a lesser degree of ovarian suppression. The four amenorrheic patients remained anorgasmic during the study. Our sample is too small to suggest a mechanism for the effects of bromocriptine on frequency of orgasm in hyperprolactinemic women. Simple amelioration of depressive mood was not sufficient, because four subjects demonstrated resolution of depression but only one reported an increase in frequency of orgasm. Cyclic ovarian function seemed to facilitate sexual function in these subjects but was not sufficient. A direct central effect of bromocriptine on libido independent of actions on affect and prolactin cannot be excluded.

One previous double-blind study documented a reduction in depression and emotional distress and improvement in self-reported libido with bromocriptine treatment of hyperprolactinemia (14), but normal control subjects were not studied, and the data were tabulated at a single point at the end of each 6-week interval.

In conclusion, we confirm the tendency to mild depression and its amelioration by bromocriptine therapy in some hyperprolactinemic women (4, 5, 14). We also describe a reduction in orgasmic potential in these women despite similar frequencies of female-initiated sexual events and a suggestion of a drug effect on libido. Mild depression and decreased orgasmic potential may be indications for therapy with a dopamine

agonist in hyperprolactinemic women, although most of our subjects did not find this medication to be of sufficient subjective benefit to desire its continuation.

- 1. Koppelman MCS, Jaffe MJ, Rieth KG, et al: Hyperprolactinemia, galactorrhea and amenorrhea: a retrospective assessment of 25 cases. Ann Intern Med 1984; 100:115–121
- 2. March CM, Kletzky OA, Davajan V, et al: Longitudinal evaluation of patients with untreated prolactin-secreting pituitary adenomas. Am J Obstet Gynecol 1981; 139:835-844
- Martin TL, Kim M, Malarkey WB: The natural history of idiopathic hyperprolactinemia. J Clin Endocrinol Metab 1985; 60:855-858
- Fava GA, Fava M, Kellner R, et al: Depression, hostility and anxiety in hyperprolactinemic amenorrhea. Psychother Psychosom 1981; 36:122–128
- Kellner R, Buckman MT, Fava GA, et al: Hyperprolactinemia, distress, and hostility. Am J Psychiatry 1984; 141:759-763
- Muller P, Musch K, Wolf AS: Prolactin: variables of personality and sexual behavior, in Psychoneuro-Endocrinology in Reproduction. Edited by Zichella L, Pancheri P. Amsterdam, Elsevier/ North Holland, 1979
- Adams DB, Gold AR, Burt AD: Rise in female-initiated sexual activity at ovulation and its suppression by oral contraceptives. N Engl J Med 1978; 299:1145–1150
- 8. Hamilton M: Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6:278-296
- Murphy DL, Pickar D, Alterman IS: Methods for the quantitative assessment of depressive and manic behavior, in The Behavior of Psychiatric Patients. Edited by Burdock EL, Sudilovsky A, Gershon S. New York, Marcel Dekker, 1982
- McNair DM, Lorr M, Droppleman LF: Profile of Mood States. San Diego, Educational and Industrial Testing Service, 1971
- Sinha YN, Selby FW, Lewis UJ, et al: A homologous radioimmunoassay for human prolactin. J Clin Endocrinol Metab 1973; 36:509-516
- 12. Nisula BC, Dunn JF: Measurement of the testosterone binding parameters for both testosterone-estradiol binding globulin and albumin in individual serum samples. Steroids 1979; 34:771–774
- Theohar C, Fischer-Cornelssen K, Akesson HO, et al: Bromocriptine as antidepressant: double-blind comparative study with imipramine in psychogenic and endogenous depression. Curr Ther Res 1981; 30:830–842
- Buckman MT, Kellner R: Reduction of distress in hyperprolactinemia with bromocriptine. Am J Psychiatry 1985; 142:242–244

### Are We Training Too Many Psychiatrists?

Joel Yager, M.D., and Jonathan F. Borus, M.D.

In contrast to the past decade's concerns about an undersupply of psychiatric manpower, the authors point out that the profession may soon be facing the prospect of an oversupply of psychiatrists. Given the present rate of producing psychiatrists, shifts in demands for psychiatric services, changing payment and access patterns regarding specialty medical care, increasing numbers of nonpsychiatrist mental health professionals, and a probable surfeit of primary care physicians, underemployment of psychiatrists may become commonplace. Future psychiatrists will likely be used more as consultants, and the profession will need fewer, but better trained, graduates. The authors present alternative proposals to deal with service needs related to such reductions.

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Over the past few years, articles in our most prestigious medical journals have announced the forthcoming glut of physicians in general and of medical specialists in particular (1–3). Health economists have demonstrated that an excess number of physicians in a community leads to unnecessary interventions and cost, and leaders in medicine foresee excessive competition for patients along with underemployment; both have let it be known that the public and the profession would be better served if the supply of physicians were decreased. In some states, actions are already being taken to reduce the physician supply; many are erecting increasingly difficult barriers to

foreign medical graduates (FMGs) wishing to obtain medical licensure (4). National legislation affecting Medicare reimbursement has been proposed that would sharply limit federal support for residency training of graduates of U.S. medical schools and virtually eliminate educational support for FMGs (5); the 1986 Budget Reconciliation Act took decisive steps in this direction.

Having just emerged from the "manpower crisis" of the early 1980s, many in psychiatry might consider it downright treasonous to suggest that we cut back on the production of psychiatrists. After all, large numbers of mentally ill patients receive little or no care. However, there is widespread concern about the quality of the psychiatrists we are producing. Many examiners for the American Board of Psychiatry and Neurology (ABPN) are shocked by the poor performance of a sizable percentage of candidates who have, presumably, completed training in accredited residency programs. One-third of the graduates of U.S. medical schools and almost 60% of FMGs do not pass the certification exams on their first try (6). Psychiatric educators are embarrassed by the poor quality of some residency programs that remain accredited despite the efforts of the Residency Review Committee. In addition, in certain areas practicing psychiatry has become increasingly difficult, with fewer available job opportunities in public, private, or academic sectors. In the view of many community practitioners, psychiatry may be on the verge of becoming a congested specialty.

In this paper we will review psychiatric manpower issues and the usual arguments for increasing the number of psychiatrists. Our analysis will show that 1) we will shortly be meeting projected psychiatric manpower needs for the future, especially in the light of probable shifts in demand for psychiatric services in the coming years, and 2) we are currently producing too many poorly trained psychiatrists as the price for providing residents' services in locales and treatment settings that have difficulty attracting qualified practitioners. We will conclude with suggestions for modi-

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fying psychiatric training and recommendations regarding the future delivery of psychiatric services.

#### **BACKGROUND**

Health planners have used a variety of methods to estimate the number of psychiatrists needed in the United States. Using figures that they admit are crude guesses, these planners have estimated a need for about one psychiatrist per 10,000 population, with ranges from 6.5 to 12.5 per 100,000 (7, 8). If one accepts these estimates, the current number of psychiatrists in the United States should be adequate. In June 1985, APA estimated that there were about 36,000 psychiatrists in the country (including psychiatric resident members) (personal communication from Carolyn B. Robinowitz, M.D., Deputy Medical Director, APA), which means that the current ratio approximates 15 psychiatrists per 100,000 population.

Using a "modified needs" formula, the 1980 report of the Graduate Medical Education National Advisory Committee (the GMENAC report) (9) suggested that by 1990 the United States would require about 38,500 general psychiatrists—8,000 more than were available in 1980. However, several facts now suggest that there will be no shortage in the 1990s. First, the number of students entering psychiatry has increased markedly— 60% more graduates of U.S. medical schools matched into psychiatry in 1986 than in 1980. Second, 1,000 to 1,200 general psychiatric residents are graduated annually (10). Third, the attrition rate for psychiatrists has been estimated to be only about 1.1%-2.0%/year due to death, illness, or retirement (personal communication, E.P. Merwin, Division of Health Professions Development, Office of Statewide Health Planning and Development, Sacramento, Calif.), and the average psychiatrist in the United States is only 44 years old and has many more work years ahead. Given these numbers, if one conservatively estimates that 500 to 600 psychiatrists are leaving while 1,000 to 1,200 new graduates are entering the manpower pool each year, the shortage of psychiatrists estimated by the GMENAC report will be nearly overcome by 1990. Even if none of the other considerations to be discussed in this paper were considered, we could still anticipate a GMENAC-defined surplus of psychiatrists beginning in the 1990s. By itself this suggests that cranking down the production of psychiatrists should have started with the PGY-1 class of July 1987.

In what follows, we will review the factors relevant to determining the appropriate number of psychiatrists, examining in turn five flawed arguments often raised in favor of increasing the supply of psychiatrists.

#### **ARGUMENT 1**

The first flawed argument is that the psychiatric needs of the population of the United States are

enormous. With the prevalence of defined psychiatric disorders in the community estimated to be from 15% to 23% (11), there might seem to be a bottomless need for psychiatric services. However, several considerations argue against dealing with the problem of need for psychiatric services solely by increasing the number of psychiatrists.

First, the prevalence of a disorder cannot be equated with a need for treatment. There is no guarantee that psychiatrists (or anyone else) know exactly how to intervene effectively for many psychiatric disorders; this is particularly true for such high-prevalence disorders as substance abuse and personality disorders (12). In addition, some disorders appear to be self-limiting even without psychiatric care.

Second, psychiatric problems such as deviant behavior, substance abuse, and delinquency have all been medicalized, and no overwhelming evidence has yet been found favoring a primary role for psychiatric rather than other social, health, or rehabilitative services for these problems.

Third, a need for treatment does not necessarily imply a demand for treatment by psychiatrists. Such a demand is a function of the desire for treatment by those with the disorders, resources available for the treatment (e.g., public or private funds for psychiatric services), and the specific requirement for a psychiatrist's services as opposed to those of other mental health providers. In some areas mental health services are regarded as elective and those who do seek mental health services often prefer to go to psychologists or social workers as "counselors," finding care with such providers less stigmatizing than going to psychiatrists (13, 14).

Fourth, a need for treatment does not necessarily define the type or amount of treatment required. The lack of standardized criteria for treatment has resulted in treatment regimens based on clinician ideology rather than patient need. Perceived shortages in psychiatric treatment manpower, therefore, are dependent on the treatment rationales selected as standard. If one believes that intensive psychoanalytic psychotherapy is the only way to treat certain patients, the perceived need for manpower will be much greater than if one believes that less manpower-intensive therapies are equally effective. Furthermore, no matter how many psychiatrists are produced, manpower resources may be diverted from the care of the more severely and chronically mentally ill to those healthier, better functioning patients who provide psychiatrists with greater professional gratification (15). Therefore, simply pumping additional psychiatrists into the system will not meet our country's psychiatric needs. If we realistically limit psychiatry's scope only to those disorders which psychiatrists can helpfully treat, those patients who want treatment from psychiatrists, and, in an unregulated medical care system, those psychiatrists willing to treat patients with substantial mental disorders, the number of psychiatrists needed diminishes substantially.

#### **ARGUMENT 2**

The second flawed argument is that we need more psychiatrists because the GMENAC report said we do. The estimates provided earlier in this paper indicate that we will soon have in the pipeline the number of psychiatrists proposed by the GMENAC report. However, the GMENAC projections did not take into account several important factors that will shape the delivery of medical and mental health care in the United States in the coming years, all of which should further reduce the number of psychiatrists needed. According to Schroeder (15), a large number of current costly practices in American medicine are likely to be curtailed by strong pressures to lower the cost of medical care. These include a reliance on too many specialists, self-referral of patients to specialists, the capacity of physicians to practice medical specialties without being Board certified, and the predominance of the fee-for-service form of practice.

Predictions for the future of medical practice (1, 2) have suggested five major trends likely to reduce the number of specialists (including psychiatrists) "demanded" by consumers. First is the rapidly increasing trend toward managed "capitated" medical care, the "HMOization" of American medicine. Such plans limit the number of visits to specialists (especially psychiatrists) and structure fiscal incentives to favor less use of medical specialists and greater use of less expensive nonphysician care providers. Second is the decreased quantity of medical care provided when cost containment is the first priority. Medicare's prospective payment system using diagnosis-related groups (DRGs) has already radically decreased hospital utilization, and similar measures are being studied to apply to outpatient and previously exempted types of care (including psychiatry).

Third is the increasing use of gatekeeper models in managed care systems. This model, currently operating in Great Britain, requires that patients see specialists only after referral from a primary care physician. In some plans already in operation in the United States, primary care providers have a strong disincentive to refer patients to specialists: fees for specialists' services come out of the same financial "pot" as do the incentive bonuses of the primary care providers. This system squeezes down the numbers of patients referred, the number of specialist visits authorized, and the fees paid for such visits.

Fourth is the trend toward horizontal and vertical integration of services by huge for-profit corporations, which will increasingly define the tasks to be performed by various types of providers and specify the numbers of each type they need (1). There will be fewer independent practice opportunities than there are today (16). Finally, the demand for scientific data supporting the effectiveness of medical and mental health interventions will increase. The degree to which patient functioning improves per unit cost of services will be highlighted (1), and we will be asked to

demonstrate changes in patients' functioning *due to treatment*, with assessment of such behavioral outcomes as personal activity, health and mental health status, role fulfillment, economic productivity, and satisfaction with care. Different types and levels of treatment by different types of providers will be compared. Even without such treatment outcome data at hand, third-party rules and algorithms are increasingly governing physician practice habits, and individual physicians no longer are as easily able to decide independently which treatment to use, how often to see patients, and when to hospitalize without external review.

Another major set of issues not adequately considered by the GMENAC report concerns the production of psychologists, social workers, psychiatric nurses, and generic "mental health therapists." Psychologists and social workers tend to cluster in the same geographic areas as psychiatrists rather than disperse out to the geographically underserved areas. According to Knesper (17), "Since physicians, psychologists, social workers, nurses, and other professionals treat the mentally ill, the contribution of all groups to the pool of mental health manpower needs to be known. Until such information is developed, expert opinion and the political process will be used to specify the number of psychiatrists needed." Although psychiatrists have been increasing in numbers, social workers and psychologists have increased at rates approximately three times those of psychiatrists over the last decade (18-20). Master's degree "therapists," mental health workers, and psychiatric technicians are also being produced in numbers far greater than are psychiatrists. Within an increasingly cost-conscious health care market, we are being undersold; and to the extent that such less costly therapists' services are perceived as equivalent, they will be used more. Like it or not, the true demand for psychiatric services in the future, especially for psychotherapy, will be heavily affected by the increased availability of such less-expensive "therapists." Organizations required to demonstrate productivity per unit cost will not find psychiatrists to be the cheapest way to go, as has already been shown in many state, county, and Veterans Administration mental health programs. Like fast foods, therapy may well be "served up" more rapidly and more cheaply, even though its quality and "digestibility" may suffer.

#### **ARGUMENT 3**

The third flawed argument is that we need more psychiatrists because many rural and urban areas don't have enough. There is clearly maldistribution of mental health professionals. Many counties in the United States have no mental health services available from psychiatrists, psychologists, or social workers (14). Although true, this statement is somewhat misleading. For example, even though California has many counties without psychiatric services, fewer than 1% of

Californians reside in counties without a psychiatrist (21). In addition, without forced geographic assignment of physicians, a concept the United States does not seem eager to embrace, there is little evidence that simply producing more psychiatrists and dumping them into the marketplace will effectively deal with the maldistribution problem. Although increasing the number of medical school graduates has resulted in an increase in all types of physicians in rural areas, this has been less true for psychiatry than for other specialties (22). Factors necessary to attract psychiatrists are often not available in either rural or underserved urban areas, including demand for their services, insurance benefits available to the population that pays for psychiatric care, educational level and belief system in the populace that sanctions psychiatric treatment, and the availability of primary care physicians who will refer patients for psychiatric care. Further, if we were to rely on a "trickle down" method to take care of maldistribution, by the time all of the geographically undesirable areas are filled by "hungry" psychiatrists, the psychiatric glut in more desirable areas would be enormous. Staffing underserved areas with National Health Service Corps psychiatrists under payback plans and providing other specific inducements such as differential insurance reimbursement to psychiatrists to explore working in these areas seem to be much more sensible and precise remedies for the maldistribution problem, surely preferable to simply flooding the market in the hope that some of the unemployed will wander to geographically underserved areas.

#### **ARGUMENT 4**

The fourth flawed argument is that we need more psychiatric residents because public sector hospitals depend on residents filling their training positions to provide needed services. We should all be outraged at the extent to which many psychiatric residents, predominantly FMGs, are unfairly exploited by programs that do not adequately prepare them to practice or to pass clinical specialty board examinations. Many of these programs are situated in large public sector settings, most in state hospitals, where the residents far outnumber the staff psychiatrists and the service load per resident is much higher than can be reasonably handled with any pretense of learning. In such settings the educational programs are often skimpy add-ons, totally inadequate to meet the residents' educational needs to master psychiatry, a new culture, and often a new language, all within the same 3- or 4-year period. Although some of these programs have university affiliations, many of these affiliations lack educational substance and help perpetuate this system by covering up the inadequacy of the training. In spite of these handicaps, large numbers of superb FMG psychiatrists make major contributions to our profession. Our concerns are focused on the quality of psychiatric education and patient care in such so-called training settings; we object both to the unfair use of predominantly FMG residents as cannon fodder in the service wars and to the inadequate education these residents often receive.

What are the facts? About 30% of all psychiatric residents in the United States are FMGs. Of the 216 residency programs listed in the 1986 edition of the Directory of Psychiatry Residency Training Programs (23), over one-quarter had half or more of their residency slots filled by FMGs. In contrast, in 17 (65%) of the 26 state-hospital-based residency programs listed, half or more of the residents were FMGs; in 12 of these 17 programs virtually all of the residents were FMGs.

Despite the inability of many public service systems to adequately prepare residents for specialty certification or modern psychiatric practice, large numbers of residents in psychiatric training status are tolerated in these settings as a way to meet pressing manpower needs inexpensively. This shortsighted policy is seriously flawed in that it inexorably leads to the community at large being flooded with large numbers of psychiatrists who have received inferior training and who are, on the average, far less likely than other psychiatrists to be able to demonstrate minimum competence.

Even if foreign-trained physicians were the only current physician manpower source available for such service systems, the assumption that they would come to these hospitals only for residency training is probably mistaken. Time-limited contract physician appointments, not "dressed up" as residency positions, would very likely be attractive to many foreign physicians who are immigrating to the United States and who need additional preparation and experience with American culture, language, and medical care practice before beginning *legitimate* specialty training. Certainly, improved training for and supervision of the services these physicians render in such settings would still be essential.

We anticipate (and in some geographic areas have started to see) that as the glut of American physicians increases and as practice opportunities in both specialties and primary care decrease, physicians will look with increased favor on salaried positions, sacrificing income and independence for regular hours and a paycheck. An oversupply of nonpsychiatric American physicians will undoubtedly stimulate many of them to start practicing psychiatry without taking residencies. Even now, the American Board of Family Medicine is considering offering specialty certification with added qualifications in areas that may increase competition with psychiatry. Marketplace competition may even lead to an increase in the number and quality of general physicians working in public sector settings as 'psychiatroids," as happened when psychiatrists were needed and other physicians were more abundant in the Armed Forces during World War II. Although one hopes that these physicians will receive adequate onthe-job training to allow them to care for patients

competently, their jobs also should not be masked as psychiatry residency programs.

#### **ARGUMENT 5**

The fifth flawed argument is that we need more psychiatrists because there are many empty leadership positions in public psychiatry. We have already shown that the "trickle down" approach, flooding the marketplace with psychiatrists, is an inefficient way to handle the maldistribution problem. It is unlikely that empty leadership positions in public psychiatry will be effectively filled by producing more psychiatrists who may initially provide line-level direct care in the public sector and then "trickle up" into systems management roles. The need for such psychiatric leadership is much more likely to be effectively dealt with if the attractiveness of such positions is increased by providing both postresidency clinician-executive training for talented psychiatrists with specific interest in public sector leadership and greater fiscal and academic incentives for such careers (24, 25).

## THE COST OF TRAINING MARGINAL RESIDENTS: LOSS OF QUALITY

A major contributor to psychiatry's low prestige as a specialty is the perception, in and out of our profession, that many psychiatrists are not high-quality professionals (26). To demonstrate this point, consider how many psychiatrists you know, and then consider to how many of them you would with confidence refer a beloved family member or friend; the latter will probably be a disturbingly small percent of the former. Concern about poor professional quality is additionally supported by the fact that requirements for psychiatric Board certification have been made less rather than more stringent over the years. Fifteen years ago ABPN certification required passing an hour-long oral examination in basic psychiatry, two live psychiatric patient examinations, and a live patient neurology examination. Now, in large measure due to the logistical problems involved in examining large numbers of candidates, only one live and one videotaped psychiatric patient examination are required. Furthermore, large numbers of psychiatrists who decline to take or who fail the Board examinations still practice without substantial negative consequences related to their lack of certification.

To illustrate the absurdity of psychiatry's position in putting manpower needs ahead of quality assurance, we will make an analogy to another profession that handles life-and-death situations. Imagine what would happen if there were too few airline pilots. Would the public sanction permitting more poorly qualified candidates to go through slipshod training programs? Would we allow such pilots to decide whether to take a watered-down certifying examination and allow

them to fly airliners with or without certification? Unlikely! Yet that is analogous to what psychiatry has done to handle its manpower needs. We are not asserting that Board certification is the gold standard that assures quality or even competence. But, we do believe that failing these examinations often reflects professional inadequacies and that allowing specialty certification to remain optional reflects a basic flaw in our profession's accountability to the public. Since keeping large numbers of marginal residents in the pipeline to satisfy service needs contributes to the likelihood that they will "pass through" substandard programs to become inadequate psychiatrists, perpetuation of this system guarantees our profession's continued low quality and prestige.

The British position on psychiatric manpower may help us as we consider our future. Much of the psychiatric care in the United Kingdom is provided by primary physicians, and a gatekeeper model is already in place—the psychiatric consultant is called in only when the primary physician believes that specialist services are necessary. The United Kingdom averages one psychiatrist per 46,000 population, about one quarter the ratio in the United States; yet, it would be hard to prove that the mental health of the British population is worse than ours due to their lower level and different use of psychiatric manpower. Although British psychiatric educators and planners believe that their current level of psychiatric manpower is too low, even at their boldest they recommend only a doubling of the supply—to about one psychiatrist per 23,000 population (27).

The British predict that their psychiatrists in the future will need to become even more specialized, having greater roles in teaching, research, and consultation than at present. We believe that economic forces at work in the United States will produce a similar result here. As we have discussed elsewhere (28), this argues for increasing the rigor of training, the standards for those we call psychiatric specialists, and the ongoing evaluation of trainees, training programs, and practitioners. To some this may be considered elitism; in our view, it is a realistic assessment of what will be required of psychiatry in the future. We should remember that the Flexner report, a historic call to substitute quality standards for the quantity production of physicians, was also called elitist in its day.

#### DANGERS OF OVERSUPPLY

Schroeder (15) and Menken (3), among others, have described the results of an oversupply of physicians. In Western Europe, where an excess of physicians already exists in several countries, it has been shown that physician incomes drop off, underemployment is common, and demoralization occurs. Medicine becomes less attractive to the best and brightest students, excessive treatment is rendered, and specialist physicians become more willing to work as primary care physi-

cians rather than as consultants. A similar oversupply of physicians has been predicted for the managed-caredominated future of American medicine (16).

For the academic medical center, physician oversupply will result in fewer referrals of paying patients from community to university hospitals (3). Since universities are among the strongest advocates for maintaining the current number of house staff (to satisfy both service needs and academic narcissism), this latter point sounds a frightening alarm: reduced referrals of paying patients to university hospitals due to oversupply of community-based physicians will not only hurt academic departments' teaching and research missions but also threaten their very economic viability.

#### **CONCLUSIONS**

In our view, the preceding discussion points toward the conclusion that we are training too many psychiatrists in general and far too many poorly prepared ones in particular. Both the profession and the public would be better served if the number of psychiatrists trained was limited to the number of high-quality training positions available and to the number of young physicians who can meet increased standards of excellent clinical practice for certification. Because many current programs that are unable to provide high-quality training would need to be closed under such a plan, we anticipate that an increase in quality would result in a decrease in the number of available training positions. Since reductions in federal funding for graduate medical education are likely to occur in the current economic climate, efforts are necessary to ensure that remaining support is channeled toward programs of assured high quality.

How can we better limit training to such quality programs? Although we recognize the need to continuously improve the validity of the Board certification process to assess competence, it is still the best national measure of clinical competence now available to our profession. Accordingly, we urge the Residency Review Committee in Psychiatry to rescind the accreditation of any residency program from which more than one-third of its graduates fail to take and pass the Boards. The American Board of Thoracic Surgery already rejects applications from surgeons who trained in programs where the Board failure rate has been excessively high. Furthermore, we would support medical licensure becoming contingent on specialty certification and differential insurance reimbursement being awarded for certified specialist versus noncertified specialist care (as already exists in Canada). Both of these developments would demand increased standards of quality and accountability by our profession. Even in advance of these changes, weak programs could be eliminated by stringent application of a tougher set of residency program accreditation requirements and appeals procedures.

We do not believe that residents are the answer for

psychiatric manpower problems in public service systems. We must no longer ignore the fact that marginal residents trained to meet a short-term service need in a specific area or institution become "free agents" after 4 years of training, fully privileged practitioners regardless of whether they have been adequately prepared or specialty certified, able to practice wherever they want, both adding to the oversupply and providing more poor care. Short-run psychiatric service manpower needs would be more effectively met by using contract physicians not being trained as resident psychiatrists and by making better use of teams of specialist consultant psychiatrists working with nonpsychiatric physicians and well-trained nonphysician mental health personnel. Various economic and clinical experiments will determine the new relationships and roles of psychiatrists with such other medical and mental health professionals in the care of the mentally ill.

In conclusion, as fiscal constraints and new medical care systems redefine the mental health market and our roles in it, we must decrease the number and increase the quality of the psychiatrists we train. Bad care for patients provided by inadequately trained psychiatrists will do more harm to our field in the eyes of both the public and our medical colleagues than all the efforts of the competing mental health professions. If we fail to discriminately cut back on the number of psychiatrists we train and better ensure that those psychiatrists we do produce can demonstrate a high standard of clinical excellence, the future attractiveness, the prestige, and, most important, the integrity of psychiatry are at risk.

- Tarlov AR: The increasing supply of physicians, the changing structure of the health-services system, and the future practice of medicine. N Engl J Med 1983; 308:1235-1244
- Geyman JP: Future medical practice in the United States: a choice of scenarios. JAMA 1981: 245:1140–1144
- Menken M: The coming oversupply of neurologists in the 1980s: implications for neurology and primary care. JAMA 1981: 245:2401–2404
- Board of Medical Quality Assurance, Department of Consumer Affairs: New Residency Training Requirement for Foreign Medical Graduates: Action Report 28:1. Sacramento, State of California, August 1985
- Inglehart JK: Reducing residency opportunities for graduates of foreign medical schools. N Engl J Med 1985; 313:831–836
- Berg L: 1984–1985 annual report of the American Board of Psychiatry and Neurology, Inc. Am J Psychiatry 1985; 142: 1255–1258
- Koran LM: Psychiatric manpower ratios: a beguiling numbers game? Arch Gen Psychiatry 1979; 36:1409–1415
- 8. Liptzin B: The psychiatrist shortage: what's the right number? Arch Gen Psychiatry 1979; 36:1416–1419
- Report of the Graduate Medical Education National Advisory Committee to the Secretary, Department of Health and Human Services, vol 2, Modeling, Research and Data Technical Panel: Publication HRA 81-652. Washington, DC, DHHS, 1980
- Crowley AE: Graduate medical education in the United States, 1984–1985. JAMA 1985; 254:1585–1593
- Myers JK, Weissman MM, Tischler GL, et al: Six-month prevalence of psychiatric disorders in three communities. Arch Gen Psychiatry 1984; 41:959–967

#### TOO MANY PSYCHIATRISTS?

- 12. Freedman DX: Psychiatric epidemiology counts. Arch Gen Psychiatry 1984; 41:931-933
- 13. Richman A, Barry A: More and more is less and less: the myth of massive psychiatric need. Br J Psychiatry 1985; 146:164-168
- 14. Knesper DJ, Wheeler JRC, Pagnucco DJ: Mental health services providers: distribution across counties in the United States. Am Psychol 1984; 39:1424-1434
- 15. Schroeder SA: Western European responses to physician oversupply: lessons for the United States. JAMA 1984; 252:373-
- 16. Abramowitz KS: The Future of Health Care Delivery in America. New York, Sanford C Bernstein & Co, July 12, 1985
- 17. Knesper DJ: How psychiatrists allocate their professional time: implications for educational manpower planning. Hosp Community Psychiatry 1981; 32:620-624
- 18. Jenkins J, Turk V: Mental health manpower, in Mental Health, United States 1983: DHHS Publication ADM 83-1275. Edited by Taube CA, Barrett SA. Rockville, Md, National Institute of Mental Health, 1983
- 19. Karls JM: Mental Health Manpower Production Study Report 1: Selected Preliminary Findings. Sacramento, California State Department of Mental Health, Human Resources Development Branch, 1984

- 20. Taube CA, Burns BJ, Kessler L: Patients of psychiatrists and psychologists in office-based practice: 1980. Am Psychol 1984; 39:1435-1447
- 21. California Psychiatrists 1980: An Analysis of Responses to the Board of Medical Quality Assurance 1980 Survey. Sacramento, Calif, Office of Statewide Health Planning and Development,
- 22. Newhouse JP, Williams AP, Bennett BW, et al: Where have all the doctors gone? JAMA 1982; 247:2392-2396
- 23. Directory of Psychiatry Residency Training Programs. Washington, DC, American Psychiatric Association, 1986
- 24. Borus JF: Issues critical to the survival of community mental
- health. Am J Psychiatry 1978; 135:1029-1035
  25. Borus JF: Teaching residents the administrative aspects of
- psychiatric practice. Am J Psychiatry 1983; 140:444–448 26. Yager J, LaMotte K, Nielsen A III, et al: Medical students' evaluation of psychiatry: a cross-country comparison. Am J Psychiatry 1982; 139:1003-1009
- 27. Crisp AH, Hemsi LK, Paykel ES, et al: A future pattern of psychiatric services and its educational implications: some suggestions. Med Educ 1984; 18:110-116
- 28. Borus JF, Yager J: Ongoing evaluation in psychiatry: the first step toward quality. Am J Psychiatry 1986; 143:1415-1419

## Growth Hormone Response to Edrophonium in Alzheimer's Disease

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Neuropathologic data from patients with Alzheimer's disease indicate the presence of neurofibrillary tangles in hypothalamic regions associated with regulation of pituitary hormone release. The authors explored the hypothesis that cholinergic projections to hypothalamic nuclei controlling pituitary growth hormone (GH) release degenerate in Alzheimer's disease. Integrity of cholinergic regulation was tested by assaying the GH response to a presynaptic cholinergic challenge. After administration of the choline esterase inhibitor edrophonium, the peak GH response was 14 ng/ml in healthy elderly control subjects and only 2 ng/ml in Alzheimer's patients. The magnitude of GH blunting was correlated with cognitive and functional deficits. Possible implications of these data for enhanced accuracy in the diagnosis of dementia are discussed.

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The clinical diagnosis of Alzheimer's disease is still largely a diagnosis of exclusion; only the histomorphologic evaluation of selected brain tissue can currently provide definitive evidence for this diagnosis.

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As brain biopsies are generally not acceptable diagnostic procedures, a diagnosis of Alzheimer's disease must remain tentative until it is confirmed or disconfirmed at autopsy. The National Task Force on Alzheimer's Disease reflected a sentiment generally shared by geriatric clinicians when it assigned primary urgency to the systematic search for a "behavioral or biological marker unique for Alzheimer's disease" (1). A specific marker could enhance diagnostic acuity and eventually permit definitive in vivo diagnosis. It would be particularly useful in making early diagnoses possible and in increasing diagnostic accuracy in cases of mixed dementias. Although a clinical diagnosis of Alzheimer's disease, in the absence of confounding comorbidity, is currently confirmed in 80%–90% of cases (2, 3), these figures are thought to be much lower in cases where other brain pathology is superimposed on Alzheimer's

Recent research has provided compelling evidence for a central cholinergic deficit in Alzheimer's disease (4, 5). The decline of histochemical markers of cholinergic function in Alzheimer brains, especially the hippocampus and temporal cortex, has been found to be correlated with the degree of cognitive decline observed in the patient before death (6, 7). The hypothalamus receives strong cholinergic projections that are thought to originate from the same cholinergic cell groups innervating the hippocampus and temporal neocortex. Hypothalamic regions receiving cholinergic input are the major sources of peptide-releasing factors that control pituitary secretion of growth hormone (GH). GH specifically is under the control of GHreleasing factor (GH-RF), localized primarily in the arcuate nucleus of the hypothalamus (8), and somatostatin, which has been localized in the paraventricular nucleus (9). These areas show the characteristic neurofibrillary tangles in patients with Alzheimer's disease (10). Furthermore, Rossor et al. (11) have shown that

in the hypothalamus of Alzheimer's disease patients, choline acetyltransferase levels, a prime indicator of cholinergic transmitter activity, are 25% lower than in the hypothalamus of normal elderly subjects. This finding supports the idea that hypothalamic cholinergic input may represent collaterals of cholinergic neurons in the nucleus basalis of Meynert and the diagonal band of Broca (11).

Our search for a potenial diagnostic marker for Alzheimer's disease was based on the hypothesis of impaired cholinergic control of pituitary hormone release in Alzheimer's disease. With a normal cholinergic neuron, a cholinesterase inhibitor such as edrophonium will increase neurotransmitter availability at the synapse by blocking transmitter degradation (12). Intravenous administration of edrophonium thus stimulates GH-RF secretion and consequently release of GH, which has been shown to be ultimately reflected in 10- to 20-fold increases of peripheral GH plasma levels (13, 14).

The present study explores whether the edrophonium-induced increase of GH plasma levels is significantly blunted in Alzheimer's disease patients compared to normal control subjects, reflecting the degeneration of central cholinergic neurons associated with the control of GH release. Because the central cholinergic deficit has also been correlated with the extent of clinical deterioration (7), we further hypothesized that the magnitude of blunting of the GH response would proportionately reflect the severity of the patients' dementia.

#### **METHOD**

Fourteen patients with Alzheimer's disease and eight healthy control subjects were recruited. All subjects were over 55 years old. In order to participate in the study, all subjects had to give informed consent. In the case of demented patients who had been declared legally incompetent, informed consent was also obtained from the court-appointed guardian. There was no significant difference (p>.10) in mean±SD age between the Alzheimer's patients (71±7 years) and the control subjects (63±11 years). The diagnosis of Alzheimer's disease employed NINCDS-ADRDA Work Group criteria (15) and was based on clinical examination and ratings on Folstein's Mini-Mental State test (16). Alzheimer's patients had to have evidence of deficits in two or more areas of cognition, score below 25 on the Mini-Mental State, and show no impairment of consciousness. Their history and physical examination had to be negative for systemic disorders or other brain diseases that could have caused secondary dementia. Patients with Alzheimer's disease who had a history of alcoholism and/or had clinical or laboratory evidence of endocrine or metabolic illness were excluded. For inclusion in the patient group, neurosyphilis had to be ruled out serologically, and CAT scans of the head had to be negative for spaceoccupying lesions, vascular accidents, and normal pressure hydrocephalus. All Alzheimer's patients scored below 18 on the Hamilton Rating Scale for Depression (17), which served as a screen for possible pseudodementia. To rule out patients with multi-infarct dementia, those with a score greater than 4 on the Hachinski Ischemic Scale (18) were excluded.

Control subjects scored 25 and higher on the Mini-Mental State and showed no clinical-functional impairment. They were either spouses of our Alzheimer's patients or healthy volunteers from the community. For the Alzheimer's and control groups, subjects who during the preceding 3 weeks had been on any medication known to affect the central cholinergic balance, especially tricyclic antidepressants and neuroleptics, were automatically excluded from participation in the study. Any pharmacologic agent reported to influence the hypothalamic-pituitary axis also rendered subjects ineligible for participation.

Tests were always done in the morning (between 8 a.m. and 1 p.m.) to minimize the impact of diurnal variation on GH release. Three baseline blood samples were drawn via an indwelling venous catheter at 15-minute intervals (-30, -15, 0) during the 30 minutes preceding administration of edrophonium. Edrophonium was administered intraveously at a dose of 0.13 mg/kg of body weight (i.e., 10 mg for a 75-kg individual, equivalent to the customary dose used in myasthenia gravis diagnostics). Edrophonium, an extremely short-acting reversible inhibitor of acetylcholinesterase, is well established in clinical practice as a safe diagnostic tool for the differential diagnosis of myasthenia gravis (19). Edrophonium is a quaternary ammonium compound that does not cross the bloodbrain barrier. The median eminence of the hypothalamus is the only anatomic structure that is involved in GH regulation and located outside the blood-brain barrier. The median eminence thus is the likely site of action of edrophonium on GH release (13). In our study, a syringe was loaded with the predetermined test dose. Then 2 mg i.v. were given, and if the subject reported no reaction (autonomic effects) in 30 seconds, the remainder of the dose was injected. Subjects occasionally described salivation, teariness, stomach grumbling and slight nausea, or light-headedness. We saw minimal drops in heart rate and blood pressure. All subjective and objective symptoms disappeared within 5-10 minutes after administration of the edrophonium. No difference between Alzheimer's patients and control subjects was found in frequency or severity of these side effects. After the edrophonium was administered, serial blood samples were drawn at 10, 20, 30, 40, 50, 60, and 80 minutes.

Alzheimer's patients were classified by severity of dementia as measured on the Folstein Mini-Mental State and in terms of the Global Deterioration Scale of Reisberg et al. (20). For the latter rating, information from relatives or caretakers and direct observation of the patient during the study were used.

Blood samples were immediately processed. They

were centrifuged, and serum GH levels were determined by radioimmunoassay by means of a double antibody procedure (21). Our within-assay coefficient of variation for this radioimmunoassay has been 4.8% over the past year. Our between-assay coefficient of variation has been 7.4%.

Mean peak elevations of GH serum levels (maximum response minus baseline level) after edrophonium challenge in the Alzheimer's disease patient sample were compared with the mean peak GH response in the control group by means of a two-tailed t test (22). In addition, we calculated the area under the curve of GH levels over time to infer comparative values of total GH response to edrophonium for patient and control groups; we derived the curvilinear function best fitted to the time-response curves for the patient and control groups, respectively. The algebraic expression could then be integrated to yield values for the areas under the curves. Linear regression analysis was employed to assess the relationship between body mass, weight, and ratings on Folstein's Mini-Mental State and Reisberg's Global Deterioration Scale and the GH response after edrophonium challenge.

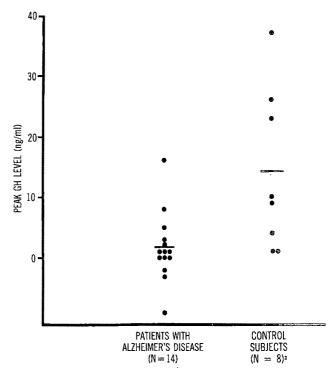
#### **RESULTS**

No correlation between age and growth hormone response to edrophonium challenge was observed in either the control subjects or the Alzheimer's disease patients. Further, no correlation between either body mass or weight and GH response was found. The mean±SD baseline GH concentrations were 6.0±7.3 ng/ml for the Alzheimer's group and 1.9±1.6 ng/ml for the control group; the difference between the two groups was not significant (t=2.04, df=15).

The GH response to edrophonium challenge in the Alzheimer's patients was significantly reduced compared to that of the control subjects (t=2.48, df=20, p<.04) (figure 1). The mean $\pm$ SD peak GH levels after stimulation were  $2\pm5.7$  ng/ml above baseline in the patient group and  $14\pm13.3$  ng/ml above baseline in the control group. In addition, the approximate total GH secretion as reflected in the area under the GH curve after edrophonium challenge indicated that the total amount of GH released was 7.5 times lower in the patients with Alzheimer's disease than in the control subjects.

The magnitude of the GH response was correlated with the patients' cognitive and functional deficit as quantified by the Global Deterioration Scale. There was a weak but statistically significant correlation between Folstein Mini-Mental State scores, which reflect formal cognitive competency, and the magnitude of GH response after challenge ( $r^2$ =.22; F=5.52, df=1, 20, p<.03). There was further a significant correlation between the Global Deterioration Scale score and the GH response to edrophonium stimulation ( $r^2$ =.24; f=6.47, df=1, 20, p<.02). Due to the nature of the scale, which assigns higher numerical

FIGURE 1. Distribution of Peak GH Levels (Maximum Response Minus Baseline Level) After Edrophonium Challenge in Patients With Alzheimer's Disease and in Healthy Control Subjects



<sup>a</sup>The mean $\pm$ SD peak GH level for the control subjects (14 $\pm$ 13.3 ng/ml) was significantly higher than for the Alzheimer's patients (2 $\pm$ 5.7 ng/ml) (t=2.48, df=20, p<.04).

ratings to greater functional deficits, the correlation between the global deterioration score and GH response was inverse.

#### **DISCUSSION**

Healthy elderly subjects in this study demonstrated a GH response to edrophonium challenge similar to that previously described in young adults (14); therefore, no age-dependent change in the hypothalamic-pituitary regulation of GH secretion associated with normal aging was identified.

In patients with Alzheimer's disease, the GH response was blunted. The hypothalamic cholinergic neurotransmission level is known to be involved in regulating pituitary GH secretion (23). The hypothalamic nuclei where regulatory peptides originate receive projections from areas that have been shown to undergo cholinergic depletion in Alzheimer's disease (11). It seems plausible to relate the observed reduction in GH response after administration of a cholinesterase inhibitor to cholinergic deficiency in the hypothalamus. Most data supporting the cholinergic hypothesis of the pathogenesis of Alzheimer's disease (24) are based on neuropathologic and neurochemical research on autopsy material. Some evidence has been accumulated that physostigmine, a cholinesterase inhibitor

which crosses the blood-brain barrier, can temporarily alleviate memory deficits in some patients with Alzheimer's disease (25). These data provide in vivo support for the functional relevance of cortical cholinergic depletion as a factor in the illness. Our data add in vivo evidence for a hypothalamic deficit in cholinergic neurotransmission. We found a correlation between the peripheral reflection of hypothalamic pathology and cognitive and functional impairments; therefore, the measurable neuroendocrine pathology appeared to be related to the patient's clinical condition.

To validate our preliminary results, the present Alzheimer's disease diagnoses must be confirmed at autopsy. Further studies comparing GH responses of patients with non-Alzheimer dementias and Alzheimer's disease patients are needed to evaluate the specificity of our findings. Additional work is also needed to determine the GH response to edrophonium challenge in milder forms of dementia, because mild to moderate cognitive decline presents a diagnostic dilemma with respect to Alzheimer's disease. Potentially, edrophonium challenge may assume clinical relevance as a component of a diagnostic marker profile to differentiate Alzheimer's disease from other types of cognitive impairment after the issues we have raised are thoroughly explored.

Despite comprehensive investigation, an etiology for dementing illness can only be identified in about 50% of patients suffering from dementia (26). Such idiopathic dementia is most often attributed to Alzheimer's disease. Recent reviews have noted how most markers or diagnostic laboratory tests associated with Alzheimer's disease have been generally disappointing (3, 27). We suggest that the relationship between the edrophonium challenge and Alzheimer's disease be more extensively characterized before any claims of its clinical and diagnostic value are made.

- Report of the Secretary's Task Force on Alzheimer's Disease. Washington, DC, US Department of Health and Human Services, 1984
- Ron MA, Toone BK, Garralda ME, et al: Diagnostic accuracy in presenile dementia. Br J Psychiatry 1979; 134:161–168
- Katzman R: Alzheimer's disease. N Engl J Med 1986; 314:964– 973
- Davies P: Neurotransmitter-related enzymes in senile dementia of the Alzheimer type. Brain Res 1979; 171:319–327
- Coyle JT, Price DL, DeLong MR: Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 1983; 219: 1184–1190
- 6. Ball MJ, Fisman M, Hachinski V, et al: A new definition of

- Alzheimer's disease: a hippocampal dementia. Lancet 1985; 1: 14-16
- 7. Perry EK, Tomlinson BE, Blessed G, et al: Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br Med I 1978; 2:1457–1459
- scores in senile dementia. Br Med J 1978; 2:1457-1459

  8. Bloch B, Gaillord RC, Brazeau P, et al: Topographical and ontogenetic study of the neurons producing growth hormone-releasing factor in human hypothalamus. Regul Pept 1984; 8: 21-31
- Finley JCW, Maderdrut JL, Roger LJ, et al: The immunocytochemical localization of somatostatin-containing neurons in the rat central nervous system. Neuroscience 1981; 6:2173–2192
- Ishii T: Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. Acta Neuropathol (Berl) 1966; 6:181–187
- Rossor MN, Iversen LL, Mountjoy CQ, et al: Arginine vasopressin and choline acetyltransferase in brains of patients with Alzheimer's type senile dementia. Lancet 1980; 2:1367–1368
- Crowley WR, Zemlan FP: Neurotransmitter systems: anatomy and pharmacology, in Neuroendrocinology of Reproduction. Edited by Adler NT. New York, Plenum, 1981
- Leveston SA, Cryer PE: Endogenous cholinergic modulation of growth-hormone secretion in normal and acromegalic humans. Metabolism 1980; 29:703-706
- 14. Bruni JF, Meites J: Effects of cholinergic drugs on growth hormone release. Life Sci 1978; 23:1351–1357
- McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology (NY) 1984; 34:485–490
- Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198
- Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62
- Hachinski VC, Iliff LD. Zilhka E, et al: Cerebral blood flow in dementia. Arch Neurol 1974; 32:632–637
- Laurence DR: Clinical Pharmacology, 4th ed. London, Churchill Livingstone, 1973
- Reisberg B, Ferris SH, deLeon MJ, et al: The Global Deterioration Scale for the assessment of primary degenerative dementia. Am J Psychiatry 1982; 139:1136–1139
- Zemlan FP, Hirschowitz J, Garver DL: Relation of psychotic symptoms to apomorphine-stimulated growth hormone release in mood-incongruent psychotic patients. Arch Gen Psychiatry 1986; 43:1162–1167
- SAS Institute: SAS User's Guide: Statistics. Cary, NC, SAS Institute, 1982
- 23. Delitalia G, Maioli M, Pacifico A, et al: Cholinergic receptor control mechanisms for L-dopa, apomorphine, and clinidine-induced growth hormone secretion in man. J Clin Endocrinol Metab 1983; 57:1145–1149
- Perry EK, Perry RH: The cholinergic system in Alzheimer's disease, in Biochemistry of Dementia. Edited by Roberts PJ. New York, John Wiley & Sons, 1980
- Mohs RC, Davis BM, Johns CA, et al: Oral physostigmine treatment of patients with Alzheimer's disease. Am J Psychiatry 1985; 142:28-33
- Marsden CH, Harrison MJG: Outcome of investigation of patients with presentle dementia. Br Med J 1972; 2:249-252
- Thienhaus OJ, Skelly MF, Hartford JT, et al: Biologic markers of Alzheimer's disease. J Am Geriatr Soc 1985; 33:715–726

# Three Patients With Concomitant Panic Attacks and Seizure Disorder: Possible Clues to the Neurology of Anxiety

Jeffrey B. Weilburg, M.D., David M. Bear, M.D., and Gary Sachs, M.D.

The authors present the cases of three patients in whom panic attacks and epilepsy appeared together. These cases illustrate various possible relationships between panic attacks and epilepsy. These relationships include 1) panic attacks representing the aura of a complex partial seizure, 2) panic attacks representing a manifestation of interictal behavior change, and 3) panic attacks and seizure coexisting independently. The authors conclude that exploration of the mechanisms operating in unusual cases like these may provide a vehicle for clarifying the neurobiological basis of anxiety.

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The paroxysms of fear and autonomic nervous system hyperactivity experienced by some patients with partial seizures (1–8) may closely resemble panic attacks. In 1962, Harper and Roth (5, 6) described a possible overlap between temporal lobe epilepsy and the "phobic anxiety-depersonalization syndrome." More recently, Brodsky et al. (1) presented a series of case reports in which refractory anxiety was considered secondary to a masked epileptiform disorder. They posited a direct connection between the panic attacks and the seizures. Another example of this unusual phenomenon was given by Dietch (8), who described a patient with cerebral tumor and panic attacks and suggested that the panic attacks represented seizures.

The similarity between the symptomatic expression of some of the fear/arousal spells induced by seizure and idiopathic panic attacks suggests the possibility that the presentation of these distinct phenomena may involve common neural mechanisms. The nature and variety of these mechanisms are incompletely addressed by existing studies (1, 5, 6, 8–13). We therefore present the cases of three patients who illustrate a

variety of possible relationships between panic attacks and seizures.

#### CASE REPORTS

Case 1. Ms. A, a right-handed secretary, had beer well until age 27, when she experienced an attack of "runny dizziness." At that time she described a sensation of sinking into her chair or moving in space accompanied by fear, dysphoria, nausea, facial flushing, palpitations, and difficulty concentrating. This episode lasted for about one minute. She returned to work, but when similar episodes recurred, she went to the emergency room. Routine physical and laboratory examinations revealed no abnormalities, and she received a diagnosis of anxiety disorder with panic attacks. On returning home, she slept deeply for 2 hours.

Similar symptoms recurred 6 months later. Ms. A's internist diagnosed a panic-anxiety syndrome. Imiprarine made her symptoms worse, low doses of alprazolam produced sedation but minimal symptomatic relief, and 5 nonths of psychodynamic therapy with a psychiatrist were not helpful.

The patient feared that she would have spells while driving, at work, or in social situations, so she confined herself to home. Her concentration and memory were impaired; irritability and lability in mood appeared.

Ms. A's symptoms corresponded closely to the DSM-III syndrome of panic attacks with agoraphobia. During neuropsychiatric consultation, however, subtle hypokinesia of the right lower face, clumsiness of the right hand, difficulty calculating, and attention deficits were noted. Neuropsychological testing suggested left temporaparietal dysfunction. Cranial CAT scan revealed prominence of the temporal horns and sulcal dilatation. Overnight EEG monitoring revealed a burst of left temporal sharp slowing of abnormal morphology during REM and several bifrontal bursts of sharp slowing during arousals.

On the basis of clinical symptoms and the abnormal EEG, a diagnosis of complex partial seizure disorder was considered. Phenytoin was started. Ms. A's symptoms began to resolve when the phenytoin reached a therapeutic level. Clorazepate, 3.75 mg, was added at bedtime for sleep.

During 2 years of treatment with phenytoin and clorazepate, Ms. A's panic episodes were extremely infrequent, tending to occur a week before menstruation. Agoraphobia resolved approximately 6 months after the panic attacks were controlled. When Ms. A stopped taking the phenytoin because she wanted to become pregnant, the panic attacks reappeared.

Case 2. Ms. B, a 23-year-old right-handed saiesperson, first experienced complex partial seizures at age 13. Her

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seizures began with a vertiginous aura, followed by a sense of strangeness in familiar surroundings (jamais vu) and a generalized tonic-clonic convulsion. Ms. B's fraternal twin and two maternal cousins who were twins all had epilepsy. The EEG revealed a right temporal spike and wave focus. Phenytoin produced good relief of these seizures, reducing their frequency to fewer than two/year.

At age 19, while taking phenytoin, she experienced new symptoms: an overwhelming sense of fear with tachycardia and diaphoresis while riding on a train. She thereafter avoided train travel. The panic states recurred on several occasions despite this travel restriction, and she soon developed a fear of walking in strange neighborhoods.

At age 22, while still taking phenytoin, she experienced several hours of fear and autonomic arousal followed by depression and suicidal rumination after losing a job she valued. Her dread in anticipation of the panic episodes led her to confine herself to her apartment. Personality changes, such as "seriousness," loss of sense of humor, decreased sexual interest, irritability, and tendency to philosophical introspection became problematic, so she sought psychiatric care and received a diagnosis of panic attacks with agoraphobia.

Considering the possibility that Ms. B's panic states were related to the preexistent seizure disorder, a neuropsychiatrist prescribed sodium valproate. At a serum level of 85 µg/ml, panic symptoms became infrequent (less than one panic attack/6 months), mild, and brief. She noted the return of sexual interest and a decrease in irritability. Phenytoin was discontinued. The vertiginous aura and secondary generalized convulsion remained under good control (fewer than one spell/year).

Case 3. Ms. C, a 32-year-old right-handed housewife, had experienced panic attacks since early childhood. These attacks could be provoked by darkness, meeting strangers, separation from her mother during the first days of school, academic examinations, and first dates. Attacks were characterized by tachycardia, shortness of breath, and a terror she likened to the fear of dying. Her daughter and a maternal aunt suffered similar symptoms.

At age 20, Ms. C experienced a single generalized tonicclonic convulsion without associated aura. The neurological examination at that time was unremarkable, and the seizure was attributed to a head injury sustained during adolescence. She remained seizure free without medication for 9 years.

At age 29, when the panic attacks became disabling, she sought psychiatric care. Panic disorder was diagnosed; the panic symptoms were ameliorated by phenelzine, 60 mg/day. However, soon after therapeutic doses of phenelzine were reached, two generalized seizures occurred. EEG revealed a left posterior slow wave focus. Phenelzine was stopped, and the panic attacks reappeared. The panic symptoms were not relieved by anticonvulsants, including sodium valproate and carbamazepine. However, when trazodone, 150 mg, and alprazolam, 1 mg/day, were added to carbamazepine, the panic attacks remitted dramatically.

#### **DISCUSSION**

Panic disorder and epilepsy typically are distinct clinical entities, each having its own particular presentation, course, and treatment. Most patients with epilepsy do not have panic attacks, and most patients with panic attacks do not have epilepsy. There are, however, unusual situations in which panic attacks and seizures exist concomitantly. Close examination of these situations affords the opportunity to consider if, and how, panic attacks and seizures may be related.

In case 1, symptoms of the panic attacks in all likelihood represented the aura of a partial seizure. Using the 1981 classification of epilepsy (14), we could consider the panic attack a complex partial seizure with psychic and autonomic symptomatology.

Several features of this case support the assertion that the panic attacks were an aspect of a seizure. First, Ms. A had measurable neuropsychological deficits (memory, calculation, and attention), prominence of the temporal horns on CAT scan, neurologic signs (face weakness and hand clumsiness), and cognitive complaints. These findings are consistent with temporal lobe dysfunction, which may be seen in patients with temporal lobe epilepsy (15). They are not typical of idiopathic panic disorder. Second, Ms. A did not respond to standard treatment for panic attacks. An adequate trial of imipramine made the panic attacks worse, although imipramine typically decreases the frequency and severity of idiopathic panic attacks. In Ms. A, the imipramine may have led to symptom escalation by lowering the seizure threshold. Alprazolam, which is usually extremely effective in treating typical panic attacks, produced little benefit here. Third, phenytoin produced symptom relief. The dramatic relief of panic symptoms by phenytoin is most consistent with the assertion that the panic attacks were seizures. The time course of the response (the panic symptoms fully cleared when the serum phenytoin level entered the therapeutic range) lends weight to this assertion. Further, when phenytoin was stopped because the patient wanted to become pregnant, identical panic spells reappeared. Fourth, clorazepate was the most useful benzodiazepine. Clorazepate has been reported to have a particular efficacy in the management of partial seizures (16). This may explain why the clorazepate was more useful than alprazolam. Finally, Ms. A had no family history of psychiatric disorder and no past history of anxiety, depression, phobia, or separation anxiety. A history of this type is often found in patients with typical panic attacks but would not be expected otherwise.

Case 2 illustrates other possible mechanisms linking seizures and panic attacks. In this patient, the panic attacks did not appear as an aura of the original seizure but arose years after the onset of seizures, at a time when interictal behavioral changes were prominent

An interictal behavior syndrome including loss of sexual interest, irritability, humorless sobriety, and philosophical preoccupation has been observed in many patients with temporal lobe epilepsy (17–19). The mechanisms of production of such changes is not established. Some investigators have suggested that the presence of a discharging epileptic focus stimulating temporal limbic structures, especially the amygdala,

may facilitate novel sensory-emotional associations (20). This phenomenon may be related to the process of limbic kindling demonstrated in experimental animals (21).

According to this view, a patient with a temporal lobe focus might develop fortuitous limbic pathways from sensory association cortices through a hyperactive amygdala into the hypothalamus. The activation of these "hyperconnections" could then lead to the experience of fear with autonomic arousal (22, 23). During the interictal period, previously neutral stimuli would be paired with dysphoric feelings and autonomic discharges, leading to specific phobias or the syndrome of agoraphobia.

An alternative mechanism to account for the progression of Ms. B's symptoms would be the development of a secondary limbic epileptic focus, possibly through the mechanism of kindling. Ictal discharges from this independent (daughter) focus could then elicit a new form of seizure associated with fear and autonomic activation. Both of these possibilities involve alteration of temporal limbic neurophysiology; the first mechanism might be described as "interictal" and the second, "ictal." The panic attacks experienced by Ms. B could be explained by either mechanism. Since phenytoin is a poor inhibitor of limbic kindling, it would not be expected to prevent development of altered sensory-limbic connections or of a daughter focus. By contrast, valproic acid is an inhibitor of limbic kindling as well as an anticonvulsant effective in the control of partial complex seizures. The beneficial effect of valproate in this patient may thus reflect either suppression of limbic excitability or control of the secondary complex partial seizure.

Since panic disorder and epilepsy are relatively common disorders, one expects to find cases in which they appear concomitantly without etiological relationship. This is illustrated by case 3. This patient had a history and course typical of panic disorder, including early childhood separation problems and performance anxiety, positive family history of anxiety disorder, and positive response to antidepressants and alprazolam. Her generalized seizures were probably acquired as the result of a head injury. Various anticonvulsants had no effect on the panic symptoms. Antipanic medication lowered the seizure threshold, but the resultant generalized convulsions bore no connection to the panic symptoms. Successful treatment required separate treatment for each disorder, with attention to the adverse rather than the therapeutic effects of the medications.

Work by Gloor et al. (22, 23), Reiman et al. (24), and Redmond and Huang (25) indicates that limbic structures—in particular, the amygdala—are involved in fear experiences generated by direct electrical stimulation. Studies in humans and animals of the anatomy and physiology of fear and anxiety generated by nonelectrical means (lactate infusion, carbon dioxide hypersensitivity) (24, 25) also implicate temporolimbic systems. The material presented here, which suggests

that panic symptoms may arise in some atypical cases from epileptic-ictal or interictal-neuronal activation of temporolimbic structures, is consistent with these studies. Continued exploration of cases like these may provide a new, useful perspective on the understanding of the neurobiology of anxiety.

- Brodsky L, Zuniga JS, Casenas ER, et al: Refractory anxiety: a masked epileptiform disorder? Psychiatr J Univ Ottawa 1983; 8:42-45
- McLachlan RS, Blume WT: Isolated fear in complex partial status epilepticus. Ann Neurol 1980; 8:639–641
- 3. Hermann BP, Dikmen S, Schwartz MS, et al: Interictal psychopathology in patients with ictal fear: a quantitative investigation. Neurology 1982; 32:7–11
- Daly DD: Ictal clinical manifestations of complex partial seizures. Adv Neurol 1975; 2:57

  –83
- Harper M, Roth M: Temporal lobe epilepsy and the phobicanxiety depersonalization syndrome, part I: a comparative study. Compr Psychiatry 1962; 3:129–151
- Roth M, Harper M: Temporal lobe epilepsy and the phobicanxiety depersonalization syndrome, part II: practical and theoretical considerations. Compr Psychiatry 1962; 3:215–226
- Stern TA, Murray GB: Complex partial seizures presenting as a psychiatric illness. J Nerv Ment Dis 1984; 172:625-627
- Dietch JT: Cerebral tumor presenting with panic attacks. Psychosomatics 1984; 25:861–863
- Hermann BP, Melyn M: Effects of carbamazepine on interictal psychopathology in TLE with ictal fear. J Clin Psychiatry 1984; 45:169-171
- Henriksen GF: Status epilepticus partialis with fear as clinical expression: report of a case and ictal EEG findings. Epilepsia 1973; 14:39-46
- Uhde TW, Boulenger JP, Roy-Byrne PP, et al: Longitudinal course of panic disorder: clinical and biological considerations. Prog Neuropsychopharmacol Biol Psychiatry 1985; 9:39–51
- Wall M, Tuchman M, Mielke D: Panic attacks and temporal lobe seizures associated with a right temporal lobe ateriovenous malformation: case report. J Clin Psychiatry 1985; 46:143–145
- Uhde TW, Post RM, Ballenger JC, et al: Carbamazepine in the treatment of neuropsychiatric disorders, in Anticonvulsants in Affective Disorders. Edited by Emrich HM, Okuma T, Mullen AA. New York, Elsevier, 1984
- Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981; 22:489–501
- Bear DM, Freeman R, Greenberg M, et al: Psychiatric aspects of temporal lobe epilepsy, in Psychiatry Update: American Psychiatric Association Annual Review, vol 4. Edited by Hales RE, Frances AJ. Washington, DC, American Psychiatric Press, 1985
- Griffith JL, Murray GB: Clorazepate in the treatment of complex partial seizures with psychic symptomatology. J Nerv Ment Dis 1985; 173:185–186
- 17. Waxman SG, Geschwind N: The interictal behavior syndrome of temporal lobe epilepsy. Arch Gen Psychiatry 1975; 32:1580–1586
- Bear DM, Fedio P: Quantitative analysis of interictal behavior in temporal lobe epilepsy. Arch Neurol 1977; 34:454

  467
- Bear DM: Behavioral changes in temporal lobe epilepsy: conflict, confusion, challenge, in Psychiatry and Epilepsy. Edited by Trimble M, Bolwig TG. New York, John Wiley & Sons, 1986
- Bear DM: Temporal lobe epilepsy—a syndrome of sensorylimbic hyperconnection. Cortex 1979; 15:357–384
- 21. Adamec RE, Stark-Adamec C: Limbic kindling in animal behavior—implications for human psychopathology associated with complex partial seizures. Biol Psychiatry 1983; 18:269—293
- 22. Gloor P, Olivier A, Quesney LF, et al: The role of the limbic

system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982; 12:129-144

23. Gloor P, Olivier A, Quesney LF: The role of the amygdala in the expression of psychic phenomena in temporal lobe epilepsy, in The Amygdaloid Complex. Edited by Ben-Ari Y. Amsterdam, Elsevier/North Holland, 1981

 Reiman EM, Raichle ME, Robins E, et al: The application of positron emission tomography to the study of panic disorder. Am J Psychiatry 1986; 143:469–477

25. Redmond DE, Huang YUH: Current concepts, II: new evidence for a locus coeruleus norepinephrine connection with anxiety. Life Sci 1979; 25:2149–2162

## Panic Disorder Precipitated by Exposure to Organic Solvents in the Work Place

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The authors describe three cases of idiosyncratic response to occupational solvent exposure, with symptoms characteristic of panic disorder (DSM-III). The specific treatment and prognostic implications of this panic-like reaction to solvents are discussed. Sodium lactate infusion is proposed as an objective test to aid in the diagnosis.

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Posure to solvents have been described for many years; they follow a typical dose-response relationship (1–4). However, less is known about idiosyncratic responses to solvent exposure that are not dose related. In this article, we suggest that organic solvent exposure can provoke recurrent symptoms that are indistinguishable from panic attacks. Furthermore, such solvent-provoked panic attacks may subsequently occur with increasing frequency and without apparent precipitants, thus fulfilling DSM-III criteria for panic disorder. Our observations are based on clinical characteristics and treatment response in three cases of DSM-III-diagnosed panic disorder with onset temporally related to acute organic solvent exposure. We

further propose the use of an objective test, sodium lactate infusion (5), as an aid in the differential diagnosis of idiosyncratic reactions to solvent exposure.

The following case reports pertain to three patients evaluated during a 2-year period at the Anxiety Disorders Clinic at Harborview Medical Center. Before being seen in our clinic, these three patients had extensive medical workups including biochemistry profile, CBC, thyroid screen, erythrocyte sedimentation rate, immunoelectrophoresis, EEG, CAT scan, pulmonary function test, skin patch test, stool analysis, neuropsychiatric testing, and neurological evaluation.

#### CASE REPORTS

Case 1. Mr. A, a 28-year-old married man, was self-referred for treatment of panic attacks. Seven years earlier, 1 month after starting a job as an aircraft mechanic, he had experienced the acute onset of confusion, disorientation, lightheadedness, tunnel vision, depersonalization, derealization, cold sweats, tachycardia, palpitations, dyspnea, tremor, and fear of dying, which lasted approximately one-half hour. At that time the patient was working with methyl ethyl ketone and toluene. He continued to experience similar reactions when in close proximity to these solvents. He also began to experience attacks outside the work place; they were most commonly associated with driving but also occurred without apparent precipitant.

Extensive medical evaluation uncovered no objective pathological finding except CAT scan evidence of mild ventriculomegaly. Because of this finding, which was not corroborated by clinical evidence of dementia or gait or urinary disturbance, the patient had been given a diagnosis of presumed normal pressure hydrocephalus, and 4 years earlier a shunt procedure had been performed. After surgery the attacks continued unabated with increasing frequency, up to

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a maximum of 20 attacks per day that usually lasted 1 to 10 minutes. Progressive phobic avoidance also occurred, presumably due to the panic attacks.

At age 12 Mr. A had experienced the onset of attacks that were similar to the presenting symptoms. At that time the attacks occurred one to two times per month over a 2- to 3-month period and then resolved. The patient's father was reported to have suffered from alcoholism and poorly specified anxiety symptoms.

As part of his evaluation for panic disorder, Mr. A had a lactate infusion (6). Normal saline was infused for 15 minutes as a control and then was changed under single-blind conditions to 0.5 M sodium lactate, 10 cc/kg over 20 minutes. Five minutes after the switch to lactate, the patient became acutely symptomatic, with symptoms indistinguishable from a typical attack. He was stabilized on nortriptyline, 150 mg/day, and alprazolam, 6 mg/day, and the attacks ceased. He continued to work in the same setting for 1 year and remained panic free.

Case 2. Ms. B, a 36-year-old married woman who had worked the past 7 years in an electronics assembly plant, was referred from the occupational medicine clinic for further evaluation. The plant had recently introduced a new process for cleaning soldered parts that used a solution containing alkylaryl polyether alcohol, organic phosphate ester, and iso-octyl phosphate acid. While standing over a container of this solution, Ms. B had experienced the acute onset of nausea, diarrhea, disorientation, visual disturbances, leg cramps, tremor, dyspnea, a lump in the throat, choking, chest tightness, weakness, disorientation, and fear of dying. The initial reaction lasted for approximately a week, with fluctuating recurrence of symptoms. For the next year she continued to experience two or three attacks per day that lasted approximately 5 minutes. The attacks were usually related to olfactory stimulation associated with supermarkets, traffic, and beauty salons but also occurred spontaneously. Ms. B experienced progressive phobic avoidance and was unable to work. She had no prior psychiatric problems or family history of psychiatric illness. Extensive medical evaluation revealed no pathological findings.

A lactate infusion was performed as previously described. After 5 to 10 minutes of receiving lactate, Ms. B experienced the onset of chest pain, coldness, difficulty in breathing, palpitations, twitching, depersonalization, difficulty speaking, and confusion. The symptoms were similar to but milder than a typical attack. The patient began a regimen of desipramine, 250 mg/day, and the attacks ceased within 2 months. Further follow-up data were not available.

Case 3. Ms. C, a 34-year-old married woman who had previously worked as a licensed practical nurse, was referred from the occupational medicine clinic for further evaluation. Five months earlier, she had experienced the acute onset of disorientation, muscle tension, dry mouth, sweating, lightheadedness, palpitations, lethargy, fatigue, and panic while working in a poorly ventilated room around paint fumes and paint thinner that contained toluene. At that time she was hospitalized overnight and given oxygen. There were at least 15 subsequent attacks that were temporally related to olfactory stimulation associated with gasoline, paint, and cleaning solutions. Ms. C also began to experience attacks that were not related to solvent exposure, including one during a bowling tournament. The frequency of attacks had increased to more than one per week, and there were progressive

symptoms of generalized anxiety and phobic avoidance. The patient quit work after maintaining steady employment for the preceding 14 years. There was no prior history of psychiatric illness or significant medical illness. The patient denied a family history of psychiatric illness. Lxtensive medical workup revealed no objective pathological findings.

A lactate infusion was performed as previously described. Ms. C remained asymptomatic throughout the infusion. Treatment with imipramine, 250 mg/day, resulted in complete resolution of attacks. Because of the subsequent onset of a bigeminal arrhythmia, which was thought to be secondary to the anticholinergic effects of imipramine, the patient was switched to trazodone, with continued resolution of attacks. The patient has since resumed work and has not experienced further attacks for 2 years while continuing trazodone treatment.

#### **DISCUSSION**

To our knowledge, this is the first description in the medical literature of panic disorder in which occupational solvent exposure is implicated as the cause. The three cases described demonstrate several factors in common. The patients were previously functioning well and were without a prior psychiatric history, with the exception of one patient who had had a brief period of panic attacks during adolescence. After the patients' initial idiosyncratic reaction to solvents, recurrent attacks were of abrupt onset, with symptoms consistent with panic attacks as defined by DSM-III. The frequency of attacks increased to more than three per 3-week time interval and occurred at times without identifiable precipitants. The symptoms became progressively disabling. Extensive physical and laboratory workup revealed no objective evidence of toxicity or allergic reaction. Co-workers did not develop similar attacks. Two of the three patients had typical symptoms provoked by lactate infusion; this is consistent with previous findings from our clinic that two-thirds of panic patients, but not depressed or normal control subjects, significantly react to lactate infusion (7). In all three cases, antidepressant treatment without psychotherapy resolved the attacks.

In a review of the literature on toxic effects of solvents, it is important to differentiate idiosyncratic responses, such as in the cases described here, from the more commonly seen dose-related exposure effects. Typically, adverse health effects from acute solvent exposure follow a dose-related pattern, starting with mild disorientation and lightheadedness and progressing to headaches and nausea and subsequently to decreasing levels of consciousness. Generally, these effects are transient, but severe high-dose exposures may result in irreversible end-organ damage that affects the peripheral nervous system, the liver, or the kidneys. Such end-organ damage can be documented with objective tests (1). In addition to these acute effects, occupational exposure to low levels of jet fuel has been reported to produce both panic-like symptoms and possible organic personality changes over a

4- to 32-year period (8). Several studies have suggested that long-term occupational exposure to solvents produces a characteristic pattern of neuropsychological testing abnormalities; these abnormalities, referred to as "solvent encephalopathy," "psycho-organic syndrome," or "painter's syndrome," are usually characterized by problems with memory and cognitive functioning and emotional lability (1–4). This reaction to chronic exposure also appears to demonstrate a doseresponse relationship.

These three cases represent a type of solvent reaction that, on the basis of physical and laboratory findings, did not appear to be dose related. Persistent neuropsychiatric sequelae of acute or intermediate low-level solvent exposure have not been well-documented with objective diagnostic tests. Such responses are less understood and infrequently described in the literature. Of interest, a similar series of patients with cocaine-induced panic disorder has been described (9). In that report, the subsequent onset of spontaneous panic attacks followed an initial idiosyncratic reaction to cocaine ingestion. The authors postulated a sensitization or kindling mechanism (10) that may also be applicable to the cases we have described.

We suggest that a recurring idiosyncratic reaction precipitated by organic solvent exposure can occur due to an underlying mechanism or vulnerability indistinguishable from that which causes panic attacks. This hypothesis has specific treatment and prognostic implications (11–13) and suggests that lactate infusion can be a useful tool for the diagnosis of such reactions to solvents.

- Baker EL Jr, Smith TJ, Landrigan PJ: The neurotoxicity of industrial solvents; a review of the literature. Am J Ind Med 1985; 8:207-217
- Flodin UY, Edling C, Axelson O: Clinical studies of psychoorganic syndromes among workers with exposure to solvents. Am J Ind Med 1984; 5:287–295
- Lindstrom K, Ruhimaki H, Hamminen K: Occupational solvent exposure and neuropsychiatric disorders. Scand J Work Environ Health 1984; 10:321–323
- 4. Axelson O, Hane M, Hogstedt C: Current aspects of solventrelated disorders, in Developments in Occupational Medicine. Edited by Zenz C. Chicago, Year Book Medical Publishers, 1980
- Pitts FN, McClure JN: Lactate metabolism in anxiety neurosis. N Engl J Med 1967; 277:1329–1336
- Cowley DS, Dager SR, Dunner DL: Lactate-induced panic in primary affective disorder. Am J Psychiatry 1986; 143:646-648
- Dager SR, Cowley DS, Dunner DL: Biological markers in panic states: lactate-induced panic and mitral valve prolapse (biological markers and panic). Biol Psychiatry 1987; 22:339–359
- 8. Struwe G, Knave B, Mindus P: Neuropsychiatric symptoms in workers occupationally exposed to jet fuel—a combined epidemiological and casuistic study. Acta Psychiatr Scand (Suppl) 1983; 303:55-67
- Post RM, Weiss SRB, Pert A, et al: Chronic cocaine administraton: sensitization and kindling effects, in Cocaine: Clinical and Biobehavioral Aspects. Edited by Fisher S, Raskin A, Uhlenhuth EH. New York, Oxford University Press, 1987
- Goddard GU, McIntyre DC, Leech CK: A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 1969; 25:295-330
- Klein DF: Delineation of two drug-responsive anxiety syndromes. Psychopharmalogia 1964; 5:397

  –408
- 12. Sheehan DV: Current views on the treatment of panic and phobic disorders. Drug Ther 1982; 12:179-193
- Klein DF: Psychopharmacological treatment of panic disorder. Psychosomatics (Suppl) 1984; 25:32–36

## Treatment of Severe Obsessive-Compulsive Disorder With Fluvoxamine

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**METHOD** 

Ten obsessive-compulsive patients received single-blind treatment with fluvoxamine, a selective serotonin reuptake inhibitor, for several weeks following at least 2 weeks of placebo. The group showed significant improvement, as measured by several clinical scales and self-ratings; six patients were judged responders. Fluvoxamine appears effective in treating severe obsessive-compulsive disorder.

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Recent findings suggest that obsessive-compulsive disorder is more common than previously believed, with a lifetime prevalence of 2%-3% of the population, higher than that for schizophrenia (1). The course of the disorder is variable but may include severe disability (2). Pharmacologic treatment strategies have been dominated by the hypothesis that dysregulation of serotonin (5-HT) neurotransmission is centrally involved in pathogenesis (3). Thus, the tricyclic clomipramine, which potently inhibits reuptake of 5-HT (4), has reportedly been effective. However, clomipramine's metabolite desmethylclomipramine also has significant effects on norepinephrine function (5).

It would be important to determine whether drugs with more selective effects on 5-HT function are also antiobsessional. Two recent studies have reported efficacy for the bicyclic fluoxetine, a selective 5-HT reuptake blocker (6, 7). However, zimelidine, a rela-

Nine inpatients and one outpatient (table 1) gave voluntary informed consent for this study. They all met DSM-III criteria for obsessive-compulsive disorder, as determined by consensus agreement of at least two research psychiatrists. In addition, their present symptoms caused severe impairment in global function. All had previously been hospitalized and had been refractory to conventional pharmacologic and/or psychotherapeutic treatment. Nine patients had been treated with tricyclic antidepressants, eight with neuroleptics, eight with high-potency benzodiazepines (alprazolam or lorazepam), four with lithium, three with monoamine oxidase inhibitors, and two each with trazodone, carbamazepine, and electroconvulsive therapy. Three had undergone prolonged courses of intensive behavior therapy. None had been treated with clomipramine. Patients with major medical or neurological disorders were excluded, as were those whose obsessive-compulsive symptoms were secondary to another psychiatric disorder. All but two pa-

Following admission, all psychotropic drugs were discontinued. Patients received placebo for at least 2 weeks (mean±SD=3.4±0.8 weeks), followed by ac-

tients (patients 1 and 10) met DSM-III symptom

criteria for major depression, which was judged sec-

ondary to their obsessive-compulsive disorder on the

basis of time course. Two patients initially admitted to

the study were excluded before active drug treatment;

one was given a rediagnosis of chronic paranoid

schizophrenia and the other of agoraphobia with panic

tively selective bicyclic 5-HT reuptake inhibitor, has yielded mixed results in treating obsessive-compulsive disorder (5, 8). To our knowledge, the present investigation is the first to demonstrate the antiobsessional effects of fluvoxamine, a unicyclic antidepressant that selectively and potently inhibits reuptake of 5-HT (9, 10). Since fluoxetine and fluvoxamine are dissimilar in terms of chemical structure, their common efficacy in obsessive-compulsive disorder is of considerable interest in evaluating the role of 5-HT dysfunction in this condition.

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TABLE 1. Ratings of 10 Obsessive-Compulsive Patients Before and After Treatment With Fluvoxamine

			Obsess	sive-Comp	oulsive Me	asures						
					Maudslev			Hamilto	on Scales		Clinical	
Patient		Age	Y-BOCS <sup>a</sup>		Inventoryb		Depression <sup>c</sup>		Anxiety <sup>d</sup>		Patient- Rated	Global Impression
	Sex	(years)	Before	After	Before	After	Before	After	Before	After	Improvement <sup>e</sup>	Scale
1	F	20	21	10	20		17	8	16	12		5
2	F	37	33	17	24		39	28	25	17	*******	5
3	M	42				8	47	43	23	23		3
4	F	42	32	11	20	19	44	9	21	7	8	5
5	F	29	27	14	25	27	25	18	22	9	7	5
6	F	39	27	18	23	18	28	16	21	11	8	5
7	M	23	28	13	18	7	30	12	21	6	9	5
8	F	<i>5</i> 8	40	25	25	18	50	29	31	16	5	4
9	M	29	24	23	19	15	30	29	20	15	9	4
10	M	29	22	23	8	13	8	9	7	11	6	3
Mean		34.8	28.2	17.1 <sup>g</sup>	20.2	15.6	31.8	20.1 <sup>h</sup>	20.7	12.7 <sup>i</sup>	7.4	4.4
SD		11.2	6.0	5.6	5.3	6.5	13.4	11.7	6.2	5.1	1.5	0.8

<sup>&</sup>lt;sup>a</sup>0=no symptoms; 40=maximal symptoms.

tive fluvoxamine for at least 4 weeks  $(5.9\pm2.0 \text{ weeks})$ . The duration of placebo and active drug treatment periods was contingent on scheduling for neuroendocrine challenge testing; variability was unrelated to clinical factors. Fluvoxamine was started at 50-100 mg/day and was increased in 50-mg increments as tolerated every 1-2 days to at least 100 mg/day ( $169\pm55 \text{ mg/day}$ ) by the end of the first week. Fluvoxamine was further titrated according to clinical state and side effects to a maximum of 300 mg/day ( $274\pm30 \text{ mg/day}$ ) in three divided doses by the end of the trial. With the exception of low-dose benzodiazepines for sleep (and, in two patients, for severe agitation), no other drugs were administered. Behavior therapy was not given.

Patients were assessed once or twice weekly by experienced raters. Obsessive-compulsive symptoms were rated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (available on request) and the Maudsley Obsessional-Compulsive Inventory (11). The Y-BOCS measures treatment-responsive changes in the severity of obsessive-compulsive symptoms; the Maudsley measure is primarily a symptom inventory. Depressive and anxiety symptoms were rated on a modified Hamilton Rating Scale for Depression and on the Hamilton Rating Scale for Anxiety. Global treatment response was assessed using the Clinical Global Impression (CGI) scale, with responders defined as patients rated much or very much improved. Patients also completed a self-report measure of global improvement. Interrater reliability of total scores was formally assessed for the Y-BOCS and the Hamilton depression scale, with intraclass correlations of .99 (p<.001) and .98 (p<.001), respectively. Patients,

clinical staff, and raters were all blind to the sequence of placebo and active medication during this single-blind trial. All tests of statistical significance were two-tailed, with the significance level set at p<.05 unless otherwise indicated.

#### **RESULTS**

Table 1 presents mean ratings for each of the patients during the last week they were given placebo and the last week of their fluvoxamine trial. For the entire sample, fluvoxamine caused highly significant decreases in scores on the Y-BOCS (mean $\pm$ SD=11.1 $\pm$ 7.1; t=4.7, df=8, p<.002), the Hamilton depression scale (mean $\pm$ SD=11.7 $\pm$ 10.7; t=3.5, df=9, p<.01), and the Hamilton anxiety scale (mean $\pm$ SD=8.0 $\pm$ 6.6; t=3.8, df=9, p<.005). Scores on the Maudsley inventory decreased, but not significantly (mean $\pm$ SD=3.0 $\pm$ 5.4; t=1.5, df=6, n.s.). As a group, patients rated themselves as moderately improved, although there was considerable variability between individuals.

On the basis of the CGI criterion, six patients were judged to be responders and four nonresponders; however, only two of the nonresponders were judged to have derived no benefit at all from treatment. No significant differences between responders and nonresponders in final fluvoxamine dose or in baseline ratings of severity on the Y-BOCS, Maudsley, or Hamilton scales were revealed by t tests. Nonresponders tended to have received fluvoxamine treatment for a longer time (50.8 vs. 35.2 days; t=2.0, df=8, p=.08).

Baseline ratings of depressive symptoms on the

b0=no symptoms; 30=maximal symptoms.

<sup>&</sup>lt;sup>c</sup>24 items, excluding obsessive-compulsive item.

d<sub>14</sub> items

e0=could not be worse; 5=unchanged; 10=could not be better.

f0=very much worse; 3=no change; 6=very much improved.

 $g_{t=4.66}$ , df=8, p<.002 (paired t test).

 $<sup>^{</sup>h}t=3.45$ , df=9, p<.01 (paired t test).

 $i_{t=3.81}$ , df=9, p<.005 (paired t test).

Hamilton depression scale and anxiety symptoms on the Hamilton anxiety scale were highly correlated with baseline ratings of obsessive-compulsive symptoms on the Y-BOCS (r=.91, p<.001, and r=.85, p<.005, respectively). Only a modest correlation was shown between baseline ratings on the Maudsley measure and the Y-BOCS (r=.58, p=.10). The magnitude of improvement on the Y-BOCS was significantly correlated with final CGI ratings (r=.73, p<.05), as well as with change in Hamilton depression (r=.86, p<.005) and anxiety (r=.81, p<.01) scores, but not with patientrated improvement or change on the Maudsley inventory. Baseline Y-BOCS scores were also correlated with magnitude of improvement on the Y-BOCS (r=.80, p<.01), the Hamilton depression scale (r=.74,p<.05), and the Hamilton anxiety scale (r=.77, p<.05) but not with change on the Maudsley inventory or with final CGI or patient ratings of improvement.

Fluvoxamine caused no major adverse reactions. Several patients developed nausea or orthostatic hypotension, both of which improved with dose reduction.

#### DISCUSSION

This trial documents the efficacy of fluvoxamine in the treatment of severely ill obsessive-compulsive patients. Significant improvement was demonstrated on ratings of obsessive-compulsive, depressive, and anxiety-related symptoms. As a group, patients also reported clinically significant subjective improvement. On the basis of conservative clinician ratings, six of the 10 patients were judged to be responders.

The present study does not distinguish between the antiobsessional and the antidepressant properties of fluvoxamine. Not surprisingly, clinical improvement was not confined to obsessive-compulsive symptoms, and the magnitude of improvement in such symptoms was highly correlated with the degree of improvement in depressive and anxiety symptoms. Moreover, the doses of fluvoxamine given and the time course of the antiobsessional response (2 to 4 weeks) seemed similar to the analogous parameters of fluvoxamine use in the treatment of primary depression (12, 13). However, nearly all of these patients had previously been refractory to adequate antidepressant trials. Patient 2, who had not responded to imipramine, phenelzine, trazodone, thioridazine, or trifluoperazine during her 19 prior hospitalizations, stated, "This is the best I've felt since it [the obsessive-compulsive disorder] started." Further clarification of the relationship between depressive and obsessive-compulsive symptoms was provided by patient 6, who maintained, "I wasn't obsessing because I was depressed. . . . I was demoralized because of the obsessions and compulsions." The degree of despair experienced by these patients was underscored by the fact that two of the nonresponders (patients 3 and 8) made suicide attempts after completion of the fluvoxamine trial. Interestingly, the correlation of baseline Y-BOCS scores with magnitude of change on the Y-BOCS and Hamilton depression and anxiety scales suggests that more severely ill patients might have experienced greater symptom improvement. At the very least, these correlations indicate that greater rated severity of obsessive-compulsive symptoms at baseline did not preclude significant improvement.

These findings are consistent with other preliminary studies documenting the efficacy of selective serotoner-gic drugs in treating obsessive-compulsive disorder (6, 7). Placebo-controlled studies are now in progress to confirm fluvoxamine's efficacy and to clarify whether a selective antiobsessional property is involved.

- Robins LN, Helzer JI, Weissman MM, et al: Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984; 41:949

  –958
- Rasmussen SA, Tsuang MT: Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 1986; 143:317–322
- Yaryura-Tobias JS, Bhagavan HN: L-Tryptophan in obsessivecompulsive disorders. Am J Psychiatry 1977; 134:1298–1299
- 4. Thoren P, Asberg M, Cronholm B, et al: Clomipramine treatment of obsessive-compulsive disorder: a controlled clinical trial. Arch Gen Psychiatry 1980; 37:1281–1289.
- Insel TR, Mueller EA, Alterman I, et al: Obsessive-compulsive disorder and serotonin: is there a connection? Biol Psychiatry 1985; 20:1174–1188
- Turner SM, Jacob RG, Beidel DC, et al: Fluoxetine treatment of obsessive-compulsive disorder. J Clin Psychopharmacol 1985; 5:207–212
- Fontaine R, Chouinard G: Fluoxetine in the treatment of obsessive compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 1985; 9:605-608
- 8. Prasad A: A double blind study of imipramine versus zimelidine in treatment of obsessive compulsive neurosis. Pharmacopsychiatria 1984; 17:61–62
- Claassen V: Review of the animal pharmacology and pharmacokinetics of fluvoxamine. Br J Clin Pharmacol 1983; 15: 3495– 355S
- Lapierre YD, Rastogi RB, Singhal RL: Fluvoxamine influences serotonergic system in the brain: neurochemical evidence. Neuropsychobiology 1983; 10:213–216
- 11. Rachman SJ, Hodgson RJ: Obsessions and Compulsions. Englewood Cliffs, NJ, Prentice-Hall, 1980
- Coleman BS, Block BA: Fluvoxamine maleate, a serotonergic antidepressant: a comparison with chlorimipramine. Prog Neuropsychopharmacol Biol Psychiatry 1982; 6:475–478
- Dick P, Ferrero E: A double-blind comparative study of the clinical efficacy of fluvoxamine and chlorimipramine. Br J Clin Pharmacol 1983; 15:4198–4258

### Meperidine-Induced Delirium

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Despite the widespread use of meperidine as an analgesic, its potential for producing delirium has been overlooked. Six cases demonstrating meperidine-induced behavioral toxicity are reported. Toxicity was more likely when meperidine was combined with cimetidine or drugs having anticholinergic activity. Discontinuation of meperidine and substitution of morphine for analgesia were usually successful in treating the delirium. Physostigmine reversed the delirium in one patient. The authors suggest that the delirium results from the excessive anticholinergic activity of meperidine or its only active metabolite, normeperidine.

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lthough developed originally as an anticholinergic A agent, meperidine is used today primarily as an analgesic. It is one of the most widely used narcotic analgesics in the United States, prescribed by approximately 60% of physicians for acute pain and by 22% for chronic pain (1). The Boston Collaborative Drug Surveillance Program Study (2) noted that 3.1% of patients developed adverse effects following intramuscular administration of meperidine; CNS effects were the most common. Several clinical reports on human subjects have described nervousness, sadness, tremors, myoclonus, and seizures (2-6). We found only one report within the past 25 years that specifically noted delirium associated with the use of meperidine (2). We now report six cases in which delirium developed with the use of meperidine.

#### **METHOD**

We reviewed the case records of 26 patients on a general surgical service during 1983–1985 who had been noted to have neuropsychiatric disturbances in association with meperidine treatment. Case identifi-

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cation of this retrospective series was accomplished by the nursing, surgical, or psychiatric staff who had been involved in the care of the patient. This series undoubtedly did not include all patients who suffered meperidine-related neuropsychiatric disturbances. For example, our series would not have included patients whose delirium had gone undetected by their primary care givers.

The patient's age, sex, vital signs, medical diagnosis, and surgical procedure were noted in each case. Subsequently, the patient's chart was reviewed by two psychiatrists (S.J.E. and B.G.) to identify the specific period and type of change in mental status and its temporal relationship to treatment with meperidine. In each instance, medical conditions that could have contributed to the neuropsychiatric symptoms were noted. If any medical etiology was a major factor, the case was excluded from the series. On this basis, 20 cases were excluded. For example, one woman who developed a delirium while taking meperidine was excluded because she also had marked hyponatremia.

#### **RESULTS**

Six cases of meperidine-induced central nervous system toxicity were identified (see table 1). All six patients experienced delirium according to *DSM-III* criteria. Two also suffered seizures. The delirium was marked by fluctuations in levels of awareness, confusion, disorientation, illusions, visual or auditory hallucinations, and in most cases persecutory delusions. In all but one case (case 1), the meperidine dose was less than the maximum dose (1200 mg/day) recommended in the 1985 *Physicians' Desk Reference*. Three days of administration were usually required before the symptoms were first evident. Once meperidine was discontinued, all patients were free of symptoms within 72 hours.

#### CASE REPORTS

Case 1. Mr. A, a 43-year-old man with Crohn's disease, was admitted for evaluation and treatment of multiple fistulae. He was treated with meperidine, 400–500 mg/day i.m., and hydroxyzine, 100 mg/day i.m., for pain relief. He also received 1200 mg/day of cimetidine. While on this regimen for several months, he suffered no untoward reac-

TABLE 1. Meperidine Toxicity in Six Surgical Patients

Pa- tient	Sex	Age (years)	Diagnosis/Surgical Procedure <sup>a</sup>	Meperidine Dose (mg/day) <sup>b</sup>	Other Medications	Neuro- psychiatric Effects	Interval Before Symptom Onset (hours)	Duration of Symptoms (hours)	Time Before Recovery After Discontinuing Meperidine (hours)
1	M	43	Crohn's disease/fistula takedown	1400	Hydroxyzine, cimetidine	Delirium, petit mal seizures	120°	48	48
2	F	66	Pancreatic carcinoma/resection	700	Doxepin, lithium	Delirium	72	72	36
3	M	22	Pancreatic pseudocyst/drainage	475	Cimetidine, hydroxyzine	Delirium, possibly 20 hypotension grand mal seizures <sup>d</sup>	72°	72	48
4	F	77	Cholecystitis/ cholecystectomy	225	None	Delirium	72	144	48
5	F	61	Small bowel obstruction/adhesion removal	300	Hydroxyzine	Delirium	96°	96	72
6	F	45	Small bowel obstruction/intestinal resection	1050	Hydroxyzine, cimetidine	Delirium	48°	48	24 <sup>c</sup>

<sup>&</sup>lt;sup>a</sup>Renal function was normal in all patients.

tions. He then underwent an exploratory laparotomy for a partial small bowel reconstruction, lysis of adhesions, and repair of multiple small bowel enterocutaneous fistulae. He developed increased pain postoperatively and received up to 1450 mg/day i.m. of meperidine and 200 mg/day of hydroxyzine. After 5 days at this dosage, Mr. A developed visual hallucinations and had several episodes of apparent petit mal seizures. He complained that the meperidine made him "crazy." Two days after discontinuing the meperidine, while his cimetidine and occasional doses of hydroxyzine were continued, his sensorium cleared completely and his seizures stopped.

Case 2. Ms. B, a 66-year-old woman, underwent abdominal surgery for a pancreatic carcinoma. She had a history of recurrent manic-depressive illness and was taking low doses of lithium carbonate (300 mg/day) and doxepin (100 mg/ day) at the time of surgery. She was lucid postoperatively and received 600-800 mg/day i.m. of meperidine to control pain. On the third postoperative day, she became progressively more confused and disoriented. She complained to family members that some of the staff were trying to kill her, while others were spreading lies about her. Psychiatric consultation was requested. The consultant (S.J.E.) recommended discontinuing meperidine and switching to morphine, as well as withholding the lithium and doxepin. He also encouraged family members to stay with her as much as possible until her delirium cleared. Within 24 hours, she was much calmer and able to respond appropriately to the staff. By 36 hours she was completely intact cognitively and recalled her experience as an "unreal nightmare." Lithium and doxepin were restarted without complications.

Case 5. Ms. C, a 61-year-old woman, entered the hospital with a small bowel obstruction. She underwent a surgical exploration that revealed adhesions from previous operations. Four days postoperatively, after receiving 300 mg/day i.m. of meperidine accompanied by 10 mg/day i.m. of

hydroxyzine, she became disoriented and confused and suffered frightening visual hallucinations of spiders climbing the walls of her room. After a psychiatric consultation, the meperidine and hydroxyzine were discontinued and morphine was started. Her hallucinations had stopped by the next day, although she remained mildly confused for 2 more days; then her sensorium cleared completely.

Case 6. Ms. D, a 45-year-old woman, entered the hospital with evidence of a small bowel obstruction. She received intravenous fluids, nasogastric suction, and meperidine, 250-350 mg/day i.m., and hydroxyzine, 25-50 mg/day i.m., for pain. She also received 1500 mg/day i.v. of cimetidine. On her ninth hospital day, she underwent an intestinal resection of a stricture. Postoperatively, she received meperidine, up to 1050 mg/day, and hydroxyzine, up to 200 mg/ day, while her cimetidine was continued at the same dose. On her 11th hospital day she became confused and disoriented, complaining to the staff that people were talking about her and "playing tricks" at her bedside. On the 12th day, a psychiatric consultation was requested after she bit through a thermometer. The consultant (S.J.E.) found her confused and agitated. Her skin was warm but not flushed, her temperature was 37.5°C, her heart rate was 100 beats per minute, and her pupils were mildly dilated. She scored 20 of a possible 30 on the Cognitive Capacity Screening Examination (7), which is the criterion level for abnormal cognition on this test. Because of the urgent need for behavioral control and our belief that meperidine-induced delirium is probably the result of increased anticholinergic activity, we administered 1 mg i.m. of physostigmine. Fifteen minutes later Ms. D was calm and stated that she felt "more like myself." On a second version of the cognitive test, she scored 29. Two hours later she again became agitated and was given another 1-mg dose of physostigmine. Her sensorium again improved. Meperidine, hydroxyzine, and cimetidine were discontinued, and morphine was used for analgesia. There were no further neuropsychiatric complications, and the next day her score

<sup>&</sup>lt;sup>b</sup>Route was intramuscular in all patients.

<sup>&</sup>lt;sup>c</sup>Took a lower dose for 1 or more weeks before the dose indicated.

<sup>&</sup>lt;sup>d</sup>Meperidine may or may not have caused the seizures.

ePhysostigmine was used.

on the cognitive test was 30. Her past history revealed that she had suffered a similar episode 4 years earlier, when she had received meperidine, promethazine, and dexbrompheniramine but no cimetidine. Her sensorium had been cleared at that time by discontinuing her medications and switching her analgesic to morphine.

#### **DISCUSSION**

Several reports have underscored the potential of meperidine to produce CNS toxicity. The Boston collaborative drug study (2) noted that CNS toxicity was the most common adverse effect following intramuscular administration of meperidine. The most common CNS symptoms were disorientation, bizarre feelings, hallucinations, and psychosis. Other studies (4, 5) have noted nervousness, hypereflexia, tremors, multifocal myoclonus, and seizures. Kaiko et al. (6) studied two groups of patients treated with meperidine. In the first group of 67 patients, 48 had evidence of CNS excitation, including nervousness, tremors, twitches, multifocal myoclonus, and seizures. In the second group of 47 patients, in whom mood alterations were assessed, Kaiko and associates noted apprehension, sadness, and restlessness but did not describe confusion, hallucinations, or delusions. Nervousness, tremors, myoclonus, and seizures correlated more highly with normeperidine plasma levels than with meperidine plasma levels.

The 2–3 days that were required for our patients to develop their CNS symptoms and have them clear also suggested that normeperidine played a major role in producing delirium. Since meperidine has a half-life in plasma of approximately 3.5 hours (8), toxicity from the parent compound should develop within the first day of treatment and should clear just as rapidly. In contrast, meperidine's only known active metabolite, normeperidine, has a half-life of 15–30 hours (5, 8); several days of treatment would be required for toxic levels to accumulate, and it would take several days for these levels to clear after the medication was discontinued.

Although used today as an analgesic, meperidine was originally synthesized in 1939 as a spasmolytic substitute for atropine (9). It has both structural and pharmacologic similarities to atropine, including anticholinergic cardiac effects (3). It has a lesser effect on the sphincter of Oddi than do other narcotic analgesics, making it useful in patients suffering from biliary colic (4). Early investigations reported atropinic effects such as flushing, dry mouth, and mydriasis, as well as CNS symptoms consistent with delirium (3, 8).

Despite early recognition of meperidine's anticholinergic activity, this has not been considered a possible basis for its CNS toxicity. For example, Blitt and Petty (10) described two cases in which patients were treated with atropine, meperidine, and lorazepam. When delirium ensued, the authors successfully treated their patients with physostigmine. They interpreted their results as indicating that physostigmine had reversed the effects of lorazepam, not those of atropine and meperidine. This report failed to mention excessive anticholinergic activity as a potential cause of neuropsychiatric toxicity.

Although meperidine has anticholinergic activity, we were unable to determine whether normeperidine has a similar action. The delirium in case 6, which followed a time course consistent with normeperidine accumulation, was reversed by physostigmine. This strongly suggests normeperidine-related anticholinergic activity as the etiological factor. It is also possible that another metabolite with anticholinergic activity could have produced the toxicity we observed. Normeperidine might also produce CNS toxicity by an opioid-related mechanism, but its seizure-inducing effects are not reversed by naloxone. In fact, its seizures are made worse by naloxone (11, 12). Hypothetically, normeperidine could also produce toxicity by a naloxone-resistant opioid effect (13).

We used physostigmine in only one case, where it was necessary to quickly control the patient's severe agitation. Simply discontinuing meperidine was successful in the other five cases; substituting morphine produced effective analgesia without CNS toxicity. This is consistent with reports that morphine does not produce the seizures or EEG changes that occur with meperidine (2, 4).

Another finding consistent with an anticholinergic basis for the delirium is that other medications given to the patients in our series have anticholinergic activity and could have potentiated the toxicity of meperidine or normeperidine. Hydroxyzine and doxepin have well-recognized anticholinergic activity (14, 15). Although lithium is infrequently considered an anticholinergic agent, its toxic effects have been attributed to central anticholinergic activity (16). Cimetidine may also have anticholinergic activity, which is consistent with a report by Mogelnicki et al. (17), who described the successful treatment of a cimetidine-induced delirium with physostigmine.

Mechanisms other than anticholinergic toxicity may account for the delirium in some of our patients. For example, cimetidine accompanied meperidine in patients 1, 3, and 6, and thus it is possible that cimetidine alone was responsible for the delirium in these patients (18, 19). In case 1, however, Mr. A's sensorium cleared once meperidine was discontinued, despite the continuation of cimetidine and hydroxyzine. The youth and excellent renal function of patient 3 diminish the likelihood that his delirium was cimetidine induced, since this form of toxicity is observed most commonly in the elderly or in individuals with renal impairment (18, 19). In case 6, Ms. D had suffered a similar episode in the past without taking cimetidine, suggesting that the current episode might well have occurred if cimetidine had not been administered.

Cimetidine could have played another role in these three cases, since it interferes with the cytochrome  $P_{450}$  and  $P_{448}$  systems' ability to metabolize drugs, including meperidine (20–22). Thus, it is possible that cimet-

idine interfered with meperidine's degradation and produced elevated levels of meperidine and normeperidine. Future studies should investigate cimetidine's effect on the metabolism of meperidine.

In summary, delirium must be considered as a possible adverse effect in patients treated with meperidine. This is particularly true for patients receiving other agents with anticholinergic activity, especially cimetidine. In suspected cases of meperidine-induced delirium, other analgesics such as morphine should be substituted.

- 1. Seitner PG, Martin BC: Survey of Analgesic Drug Prescribing Patterns. Washington, DC, Drug Abuse Council, 1975, pp 6-7
- Miller RR, Hershel J: Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol 1978; 18:180-189
- Goodman LS, Gilman A (eds): The Pharmacological Basis of Therapeutics, 2nd ed. New York, Macmillan, 1956, pp 263– 265
- Jaffe JG, Martin WR: Opioid analgesics and antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th ed. Edited by Gilman AG, Goodman LS, Gilman A. New York, Macmillan, 1980
- Szeto HH, Inturissi CE, Houde R, et al: Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure. Ann Intern Med 1977; 86:738-741
- Kaiko RF, Foley KM, Grabinski PY, et al: Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol 1982; 13:180–185
- Jacobs JW, Bernhard MR, Delgado A, et al: Screening for organic mental syndromes in the medically ill. Ann Intern Med 1977; 86:40–46
- Stambaugh JE, Wainer IW, Sanstead JK, et al: The clinical pharmacology of meperidine—comparison of routes of administration. J Clin Pharmacol 1976; 16:245–256

- Eisleb VO, Schnaumann O: Dolantin, ein neuartiges spasmolytickum und analgetikum. Deutsche Medizinische Wochenschrift 1939; 55:967–968
- Blitt CD, Petty WC: Reversal of lorazepam delirium by physostigmine. Current Researches in Anesthesia and Analgesia 1975; 54:607–608
- Gilbert PE, Martin WR: Antagonism of the convulsant effects of heroin, d-propoxyphene, meperidine, normeperidine, and thebaine by naloxone in mice. J Pharmacol Exp Ther 1975; 192:538-541
- Tortella FC, Cowan A, Alder MW: Studies on the excitatory and inhibitory influence of intracerebroventricularly injected opioids on seizure thresholds in rats. Neuropharmacology 1984; 23:749-754
- Cowan A, Geller EB, Adler MW: Classification of opioids on the basis of change in seizure threshold in rats. Science 1979; 206:465–467
- Loew ER: Pharmacologic properties of antihistamines in relation to allergic and non-allergic disease. Med Quarterly 1952; 3:1-6
- 15. Snyder SH, Yamamura HI: Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiatry 1977; 34:236–239
- Kauba S, Richelson E: Anticholinergic effects of lithium. N Engl J Med 1984; 310:989–990
- Mogelnicki ŚR, Waller JL, Finlayson DC: Physostigmine reversal of cimetidine-induced mental confusion. JAMA 1979; 241: 826–827
- Weddington WW, Muelling AE, Moosa HH: Adverse neuropsychiatric reactions to cimetidine. Psychosomatics 1982; 23:49-53
- Strauss A: Cimetidine and delirium: assessment and management. Psychosomatics 1982; 23:57–62
- 20. Rendic S, Sunjic V, Toso R, et al: Interaction of cimetidine with liver microsomes. Xenobiotica 1979; 9:555-564
- Somogyi A, Gugler R: Drug interactions with cimetidine. Clin Pharmacokinet 1982; 7:23–41
- Knodell RG, Holtzman JL, Crankshaw DL, et al: Drug metabolism by rat and human microsomes in response to interaction with H<sub>2</sub> receptor antagonists. Gastroenterology 1982; 82:84-88

### Onset of Gilles de la Tourette's Syndrome Before 1 Year of Age

Larry Burd, M.S., and Jacob Kerbeshian, M.D.

The authors report on three patients in North Dakota with an apparent onset of Gilles de la Tourette's syndrome before 1 year of age. Infantile onset may occur in 4.1% of the child patients with Tourette's disorder in that state. It is suggested that the diagnostic criteria for Tourette's disorder be revised to include patients who develop the illness before they are 1 year old.

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illes de la Tourette's syndrome is a condition Characterized by multiple motor and vocal tics with a waxing and waning course (1, DSM-III). The current diagnostic criteria for Tourette's disorder require that the condition be present for more than 1 year, that the tics have a waxing and waning course with temporary suppressibility, and that onset occur between 2 and 15 years of age. In the past few years there have been several reports of Tourette's disorder patients with a late onset of motor and vocal tics (2, 3). Some of these patients met the criteria for Tourette's disorder except for age at onset (4). An early onset of the tics of Tourette's disorder is more difficult to document. Rhythmic motor activities (stereotypies) have been reported to be common in children under age 5 (5, 6), and abnormal head movements in young children are also reported to be common (7). Children with onset of Tourette's disorder before age 2 are rarely reported in the literature. Comings and Comings (8) reported that only two of 250 consecutive patients had an onset between 1 and 2 years of age. We recently encountered three patients with an onset of the disorder in early infancy. These cases of infantile onset are being reported for the benefit of clinicians working with Tourette's disorder patients.

#### **METHOD**

We have reported elsewhere (9, 10) an ongoing study of Tourette's disorder in North Dakota. The following is a brief summary of the method for that study. We contacted each pediatrician, psychiatrist, neurologist, and family practice physician in the state, the North Dakota Tourette Syndrome Association, and the state's comprehensive developmental disabilities evaluation center, asking them to supply us with the birth dates, initials, and sex of patients who met DSM-III criteria for Tourette's disorder. Those who did not respond were then contacted by telephone. The final response rate was in excess of 95%. This procedure led us to six cases of the disorder that we had not already seen in our population of 89 cases.

For the present study we adhered strictly to the DSM-III criteria for Tourette's disorder except for age at onset after 2 years. All patients whom we had diagnosed earlier as having the disorder but who did not meet these strict criteria (six children and 10 adults) were excluded from this study. This initial procedure identified two siblings who met these criteria. A search through the charts of 73 other patients revealed a third patient with a possible onset of Tourette's disorder before 2 years of age. We report the representative case histories of the two siblings.

#### CASE REPORTS

Case 1. Alice was born at term following an uncomplicated pregnancy, labor, and delivery. She went home from the hospital at 3 days of age and had an uneventful neonatal course. When she was approximately 4 months old, her mother noted that she was exhibiting a number of unusual movements and recorded these in her baby book. Initially, she began squinting, which lasted for a month or so, and then an accompanying shoulder shrugging began. In the following month grimacing, head turning, and spasmodic grunting were observed; the mother described all these movements in the baby book. The movements persisted, with one disappearing only to be replaced by another. Lip smacking appeared and was replaced by an "eh-eh" sound. The movements were abrupt and intrusive. The mother noted that they "just appeared suddenly" and were not in the service of play or what she felt was normal activity for an infant. By approximately 14 months Alice was demonstrating both echolalia and echopraxia. This "parroting" was

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initially thought to be just play in the course of normal development, but it persisted and became a considerable problem. The echopraxia continued until the child's fifth birthday. Multiple motor and vocal tics persisted.

The mother consulted several physicians and was repeatedly reassured that she was worrying excessively about these "habits." At 14 years of age, when she was in the eighth grade, Alice underwent a psychological evaluation. Upon noting her tics, the psychologist referred her to a child psychiatrist, who made a diagnosis of Tourette's disorder. As her tics were interfering substantially with her academic progress, pharmacotherapy was recommended. She was initially treated with clonidine, 0.05 mg/day, targeting primarily her compulsive symptoms and cognitive difficulties. Clonidine was discontinued because of its unacceptable side effects. A subsequent trial of haloperidol led to a reduction in tics but did not enhance her academic performance. Haloperidol was also discontinued, as Alice was not subjectively bothered by her tics.

Case 2. Bob, Alice's brother, was also born after an uncomplicated pregnancy, labor, and delivery, and he also had tics starting before 1 year of age. His mother was quite concerned that he and his sister had inherited a serious disease and would take both children to their physician, pointing out these movements. The movements were either ignored by physicians, or the children would not exhibit them during their office visits. Bob began having tics at approximately 4 months of age, with head turning to the right, then shoulder jerking and grimacing. Later, he began to squint and make grunting sounds; the grimacing continued. The mother indicated that these movements were distinctly different from those she had seen in other infants and were quite similar to the movements exhibited by his sister.

Through the years, multiple motor and vocal tics persisted. For example, rather noticeable lip smacking would wane, only to be replaced by a persistent grunting. In the seventh grade, Bob was referred to a child psychiatrist, and a diagnosis of Tourette's disorder was made. Treatment with haloperidol, 0.05 mg/day, led to a dramatic reduction in his tics, marked improvement in his academic performance, a sharp reduction in his explosive temper, and great improvement in his ability to relate to his peers.

After the mother saw a patient education film on Tourette's disorder, she again affirmed that tics had been present in both Alice and Bob since early infancy. We consider her to be a reliable developmental historian. No other members of the immediate family are known to have Tourette's disorder or tics, and there is no other known history of major mental or neurologic disease in the extended family.

#### RESULTS AND DISCUSSION

These case reports are presented to alert clinicians to the fact that infantile onset of Tourette's disorder is possible. It is striking that two of our three patients were siblings and that the family history was otherwise devoid of tic disorders. Although the three patients we have mentioned exhibited definite primary tics and impairing secondary cognitive, emotional, and behavioral symptoms, the severity of their symptoms was not striking compared to that of a great number of our patients with a later onset of Tourette's disorder. Their very early onset of symptoms does not appear to have been predictive of severity or impairment. Two of these patients met the *DSM-III* criteria for Tourette's disorder (except for onset after age 2) by 18 months of age (including a duration of 1 year) and the other by 21 months of age.

The Census Bureau for the State of North Dakota indicated that there were 140,580 children between the ages of 6 and 18 in the state in 1980 (11). In our sample of 73 children (6 through 18 years of age) with Tourette's disorder, three, or 4.1%, had an onset before 2 years of age.

The rationale for using 2 years of age in DSM-III as a cutoff for the onset of tics is unclear. There are no apparent neurophysiological milestones that occur at this age which would represent a developmental threshold for the emergence of tics (12). The diagnosis of Tourette's disorder should not be excluded on the basis of an early onset of tics. These cases support the change in criteria for Tourette's disorder in the revised edition of DSM-III (DSM-III-R), which requires that the onset of tics be only before 21 years of age.

- Shapiro AK, Shapiro E, Brunn RD, et al (eds): Gilles de la Tourette Syndrome. New York, Raven Press, 1978
- Lang AE, Moldofsky H, Awad AG: Long latency between the onset of motor and vocal tics in Tourette's syndrome. Ann Neurol 1983; 14:693-694
- Marneros A: Adult onset of Tourette's syndrome: a case report. Am J Psychiatry 1983; 140:924–925
- 4. Sutula T, Hobbs WR: Senile-onset vocal and motor tics. Arch Neurol 1983; 40:825–826
- Werry JS, Cartielle J, Fitzpatrick J: Rhythmic motor activities (stereotypies) in children under five: etiology and prevalence. J Am Acad Child Psychiatry 1983; 22:329–336
- Thelen E: Rhythmical behavior in infancy: an ethological perspective. Developmental Psychol 1981; 17:237–257
- Nelĥaus G: Abnormal head movements of young children. Dev Med Child Neurol 1983; 25:384

  –389
- Comings DE, Comings BG: Tourette syndrome: clinical and psychological aspects of 250 cases. Am J Hum Genet 1985; 37: 435–450
- 9. Burd L, Kerbeshian J, Wikenhaiser M, et al: A prevalence study of Gilles de la Tourette syndrome in North Dakota school-aged children: J Am Acad Child Psychiatry 1986; 25:552–553
- Burd L, Kerbeshian J, Wikenhaiser M, et al: Prevalence of Gilles de la Tourette's syndrome in North Dakota adults. Am J Psychiatry 1986; 143:787-788
- 11. Department of Census: General Population Characteristics of North Dakota (document number PC-80-1-B36). Bismarck, Bureau of Commerce. 1980
- Bureau of Commerce, 1980

  12. Cohen D, Detlor J, Shaywitz B: Interaction of biological and psychological factors in the natural history of Tourette syndrome: a paradigm for childhood neuropsychiatric disorders, in Advances in Neurology, vol 35: Gilles de la Tourette Syndrome. Edited by Friedhoff AJ, Chase TN. New York, Raven Press,

### The DST and Posttraumatic Stress Disorder

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The dexamethasone suppression test (DST) was administered to 28 male combat veterans with posttraumatic stress disorder. Six subjects (21%) were nonsuppressors. The nonsuppression rates for the subgroups with and without major depressive disorder according to the Research Diagnostic Criteria were 50% and 6%, respectively. The authors conclude that cortisol nonsuppression is rare in posttraumatic stress disorder unless there is concomitant major depression.

(Am J Psychiatry 1987; 144:1068-1071)

The concept of posttraumatic stress disorder has a long history in both military and civilian medicine (1, 2), but formal recognition and diagnostic criteria (DSM-III) have only recently been given. Posttraumatic stress disorder is classed among the anxiety disorders in DSM-III, yet the diagnostic signs and symptoms required for this diagnosis include many features usually associated with depression: markedly diminished interest in activities, detachment from others, constricted affect, guilt, impairment of memory and concentration, sleep difficulties, and recurrent thoughts of death.

The dexamethasone suppression test (DST) has been an important tool in research on depressive disorders, and there has also been interest in the DST results from patients with various anxiety disorders (3–12). To our knowledge, the only published result of DSTs given to patients with posttraumatic stress disorder was Evans et al.'s incidental finding (13) of normal cortisol suppression in response to dexamethasone challenge in two inpatients with posttraumatic stress disorder. Data on the frequency of DST nonsuppression among patients with posttraumatic stress disorder, especially in relation to concurrent depression, may elucidate any relationship between these two disorders and add to

the present understanding of posttraumatic stress disorder as defined by *DSM-III*.

#### **METHOD**

Subjects with active symptoms of posttraumatic stress disorder were recruited from the mental hygiene clinic and psychiatry inpatient service of a Veterans Administration medical center on the basis of clinical interviews and charts indicating DSM-III diagnoses of posttraumatic stress disorder. Many of these patients were culled from long-term individual and group treatment programs involving combat veterans and former prisoners of war from the Korean War and World War II. The criteria for inclusion in the study were male sex, age between 18 and 75 years (the oldest patient was 68), ability to give informed consent, and presence of unstable medical illness. The customary exclusion criteria for the DST were observed, including presence of current alcohol abuse or withdrawal (14). Twentyeight subjects completed the protocol. The largest group (N=14) had been exposed to combat in World War II, five were veterans of the Korean War, and nine had fought in Vietnam.

All subjects were instructed to taper and finally discontinue any psychotropic medication, including antidepressants, anxiolytics, and sedative-hypnotics. The outpatients were drug free for 14 days; because of the impracticality of a 2-week washout period on the hospital unit, the inpatients were drug free for 7 days. Two outpatients were unable to tolerate the reduction of medication, and only their prewithdrawal DST results are included here (see Results section).

On the day of testing, the subjects met with one of us (H.K., J.D., or K.M.) for a structured interview including the Schedule for Affective Disorders and Schizophrenia (SADS, parts I and II) (15) and a structured posttraumatic stress disorder interview with operational definitions and rating anchor points for each of the DSM-III criteria. (This interview was developed by us and is available on request. In a study of the interrater agreement on the diagnoses of 12 patients, kappa values of 0.84, 0.91, and 0.93 were achieved for each rater pair.) Scores on the Hamilton Rating Scale for Depression were extracted from the SADS data with the algorithm described by Endicott et al. (16).

Each subject was given a 1-mg oral dose of dexa-

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TABLE 1. Clinical and DST Data for 28 Men With Posttraumatic Stress Disorder

						Hamilton				ostdexai 0 p.m. C	Prevalence of Nonsuppression (cort.sol ≥5			
		Age (years)		Inpatients		Depression Score			μg/dl		nmol/liter		μg/dl) <sup>a</sup>	
Group	N	Mean	SD	N	%	Mean	SD	Range	Mean	SD	Mean	SD	N	%
Total Without major de-	28	53.9	11.2	11	39	23.3	8.6	8–39	2.58	2.50	71.0	69.0	6	21
pressive disorder With major de-	18	54.1	12.1	4	22	18.2	7.6	8-33	1.86	1.87	51.0	52.0	1	6
pressive disorder	10	53.5	9.8	7	70	29.7 <sup>b</sup>	4.9	24-39	3.83	3.15	93.0	87.0	5	50

<sup>a</sup>Significant difference among groups ( $\chi^2$ =5.49, df=1, p<.05).

methasone at 11:00 p.m., and the results were based on a 4:00 p.m. blood sample drawn in a 7-ml Vacutainer without additive. The sample was centrifuged at 2000 g. The plasma was removed and stored at  $-20^{\circ}$ C until the time of assay. Cortisol determinations were made with a commercially available radioimmunoassay kit (Nuclear Medical Laboratories, Irving, Tex.). Our laboratory has reported intra-assay coefficients of variation of 10.0% and 9.3% for cortisol levels of 5.64 μg/dl (156.0 nmol/liter) and 13.60 μg/dl (375.0 nmol/ liter), respectively (17). The manufacturer reports interassay coefficients of variation of 8.5% for a cortisol level of 7.1 µg/dl (196.0 nmol/liter) and 6.9% for 13.0 µg/dl (359.0 nmol/liter). A cortisol value of 5 µg/dl (138.0 nmol/liter) or above was used to indicate nonsuppression (14). The DST assays were performed by personnel blind to the clinical data.

#### **RESULTS**

Relevant demographic, clinical, and neuroendocrine data are shown in table 1. At the time of interview, 24 of the 28 patients each had at least one other psychiatric diagnosis according to the Research Diagnostic Criteria (RDC) (18): major depressive disorder (N=10), intermittent depressive disorder (N=7), generalized anxiety disorder (N=5), agoraphobia (N=8), social phobia (N=3), mixed phobia (N=1), and minor depressive disorder (N=2).

Of the 10 patients who met the RDC for current major depressive disorder, six were diagnosed as having endogenous depression according to the RDC and according to the Newcastle Endogenous Depression Index (19). In each case the onset of depression occurred after, but was not necessarily related to, the traumatic event.

The mean  $\pm$ SD Hamilton depression score for the six endogenously depressed subjects was 31.6 $\pm$ 5.4 (range=24–39); the score for the four nonendogenously depressed subjects was 26.0 $\pm$ 2.7 (range=25–29). As shown in table 1, the mean Hamilton depression score for the total group of depressed subjects was significantly higher than that of the 18 subjects without depression.

An overall DST nonsuppression rate of 21% was found. The nonsuppression rate associated with each concurrent diagnosis was determined. The rate was 0% (none of four) for the patients with no other diagnoses, 11% (one of nine) for those with intermittent or minor depressive disorder, 0% (none of five) for the patients with generalized anxiety disorder, 17% (two of 12) among those with agoraphobia, social phobia, or mixed phobia, and 50% (five of 10) for the patients with major depressive disorder. Of all 18 of the subjects without major depressive disorder, nonsuppression occurred in only one (6%). He was a 66-year-old outpatient with a Hamilton depression score of 24.

In the five patients with major depressive disorder who exhibited nonsuppression, the depression was invariably of the endogenous type according to the Newcastle scale. When DSM-III criteria were applied to the 10 subjects with major depressive disorder, three patients were found to be melancholic; all of them were nonsuppressors. Three of the seven nonmelancholic patients were also nonsuppressors. The nonsuppressors were significantly more depressed than the suppressors; their mean±SD Hamilton scores were  $30.1\pm6.1$  and  $20.2\pm7.9$ , respectively (t=3.3, df=26, p<.001). There was a nonsignificant difference in mean postdexamethasone cortisol level between the subjects with and without major depressive disorder, and the depressed group showed a significantly higher frequency of nonsuppression (see table 1).

Neither of the two subjects maintained on psychotropic medication (phenelzine in both cases) was diagnosed as depressed. Both were suppressors of cortisol; their 4:00 p.m. cortisol values were 1.22 and 1.20  $\mu g/$  dl (34.0 and 33.0 nmol/liter), and their Hamilton scores were 13 and 24, respectively. Exclusion of these individuals from the analysis raises the percentage of nonsuppression to 23% for the entire group and to 6.25% for the nondepressed subjects.

The weight loss ratings indicated that four of the six nonsuppressors reported losing weight during the present episode of illness; only four of the 22 suppressors had lost weight. In two nonsuppressors the weight loss exceeded 5 lb., whereas this was not the case for any of the suppressors.

bSignificantly different from mean score of subjects without major depressive disorder (t=4.87, df=26, p<.001).

#### **DISCUSSION**

Our findings reaffirm the general impression that DST nonsuppression is frequently associated with melancholia. The prevalence of nonsuppression (6%) in the 18 patients with posttraumatic stress disorder who did not currently manifest major depressive disorder approximated that of the general population.

The authors of DSM-III defined posttraumatic stress disorder as an anxiety disorder. There have been reports on the DST suppression rates associated with other DSM-III anxiety disorders, including generalized anxiety disorder, agoraphobia with and without panic attacks, and obsessive-compulsive disorder. Detailed review of this literature is beyond the scope of this paper, but at present no clear trend has emerged to suggest that cortisol nonsuppression is characteristic of the anxiety disorders as a group or of any particular anxiety disorder. In our sample of 28 men with posttraumatic stress disorder, 14 (50%) had at least one other anxiety disorder diagnosis. Among the 18 patients without current major depressive disorder, nine (50%) met criteria for one concurrent anxiety disorder and three (17%) had two additional anxiety diagnoses. All but one were suppressors of cortisol. The single nonsuppressor without major depressive disorder met the RDC for both intermittent depressive disorder and agoraphobia. On the basis of these findings we are unable to demonstrate a significant association between the DSM-III diagnosis of posttraumatic stress disorder and DST nonsuppression in the absence of concurrent major depression.

Other factors—including weight loss, previous diagnosis of alcoholism, and hospital status—may have contributed to the abnormal DST results among our subjects. The shorter drug washout period for inpatients raised the possibility of pharmacologic "rebound" from antidepressants or of drug withdrawal as a factor in cortisol response (20, 21).

We used Carroll et al.'s suggested cortisol cutoff value of  $5.0~\mu g/dl$  as indicative of hypothalamic-pituitary-adrenal axis abnormality (14). Altering the cutoff value to  $6.0~\mu g/dl$  (166 nmol/liter) would change one of the nonsuppressors with major depressive disorder to a suppressor. The nonsuppression rate of the entire sample would drop to 18%, and nonsuppression among the major depressive disorder group would fall to 40%.

We previously demonstrated an association between posttraumatic stress disorder and major depression (22), but the strength of the association remains unclear. Of the subjects in this study, 21% were endogenously depressed. Sierles et al. (23) found only an 8% prevalence of endogenous depression in a sample of 25 hospitalized patients with posttraumatic stress disorder, and still fewer of their patients would have met the DSM-III criteria for melancholia. On the other hand, Pitts (24) stated that "most patients with [posttraumatic stress disorder] are endogenous depressives with obsessive preoccupations." Our clinical and labora-

tory findings do not support Pitts's conclusion, but we cannot rule out the possibility that a subgroup of such patients may be included among those meeting the DSM-III criteria for posttraumatic stress disorder. The 36% current prevalence and 41% lifetime incidence of major depressive disorder we previously found (22) among subjects with posttraumatic stress disorder underline the importance of considering the diagnosis of major depression whenever patients are evaluated for posttraumatic stress disorder.

- Kormos HR: The nature of combat stress, in Stress Disorders Among Vietnam Veterans. Edited by Figley CR. New York, Brunner/Mázel, 1978
- Andreasen NC: Posttraumatic stress disorder, in Comprehensive Textbook of Psychiatry, 3rd ed, vol 2. Edited by Kaplan HI, Freedman AM, Sadock BJ. Baltimore, Williams & Wilkins, 1980
- Sheehan DV, Claycomb JB, Surman OS, et al: Panic attacks and the dexamethasone suppression test. Am J Psychiatry 1983; 140:1063-1064
- Curtis GC, Cameron OG, Neese RM: The dexamethasone suppression test in panic disorder and agoraphobia. Am J Psychiatry 1982; 139:1043-1046
- Cottraux JA, Bouvard M, Claustrat B, et al: Abnormal dexamethasone test in primary obsessive-compulsive patients: a confirmatory report. Psychiatry Res 1984; 13:157–165
- Peterson GA, Ballenger JC, Neese R, et al: The dexamethasone suppression test in agoraphobia. J Clin Psychopharmacol 1985; 5:100-102
- Avery DH, Osgood TB, Ishiki DM, et al: The DST in psychiatric outpatients with generalized anxiety disorder, panic disorder, or primary affective disorder. Am J Psychiatry 1985; 142:844

  –848
- 8. Insel T, Kalin NH, Guttmacher JB, et al: The dexamethasone suppression test in patients with primary obsessive-compulsive disorder. Psychiatry Res 1982; 6:153–160
- Coryell W, Noyes R, Crowe R, et al: Abnormal escape from dexamethasone suppression in agoraphobia with panic attacks. Psychiatry Res 1985; 15:301–311
- Lieberman JA, Kane JM, Sarantakos S, et al: Dexamethasone suppression tests in patients with obsessive-compulsive disorder. Am J Psychiatry 1985; 142:747-751
- Monteiro W, Marks IM, Noshirvani H, et al: Normal dexamethasone suppression test in obsessive compulsive disorder. Br I Psychiatry 1986: 148:326-328
- J Psychiatry 1986; 148:326-328

  12. Schweizer EE, Swenson CM, Winokur A, et al: The dexamethasone suppression test in generalized anxiety disorder. Br J Psychiatry 1986; 149:320-322
- Evans DL, Burnett GB, Nemeroff CB: The dexamethasone suppression test in the clinical setting. Am J Psychiatry 1983; 140:586-589
- Carroll BJ, Feinberg M, Greden JF, et al: A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Arch Gen Psychiatry 1981; 38:15–22
- Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia (SADS), 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
- Endicott J, Cohen J, Nee J, et al: Hamilton Depression Rating Scale: extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1981; 38:98-103
- Ritchie JC, Carroll BJ, Olton PR, et al: Plasma cortisol determination for the dexamethasone suppression test. Arch Gen Psychiatry 1985; 42:493-497
- Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773–782

- Carney MWP, Roth M, Garside RF: The diagnosis of depressive syndromes and the prediction of ECT response. Br J Psychiatry 1965; 111:659-674
- Dilsaver SC, Greden JF: The effect of antidepressant withdrawal on the dexamethasone suppression test. Psychiatry Res 1985; 14:111-122
- Kraus RP, Grof P: Discontinuation of drugs and DST results (letter). Am J Psychiatry 1985; 142:518
- Davidson J, Swartz M, Storck M, et al: A diagnostic and family study of posttraumatic stress disorder. Am J Psychiatry 1985; 142:90-93
- 23. Sierles FS, Chen J-J, McFarland RE, et al: Posttraumatic stress disorder and concurrent psychiatric illness: a preliminary report. Am J Psychiatry 1983; 140:1177–1179
- 24. Pitts FN Jr: Special section: posttraumatic stress disorder: editorial. J Clin Psychiatry 1985; 46:373

# An Open Trial of L-Tyrosine in the Treatment of Attention Deficit Disorder, Residual Type

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To elucidate the role of catecholamines in attention deficit disorder, the authors conducted an open 8-week trial of L-tyrosine in 12 adults with attention deficit disorder, residual type. Eight showed marked to moderate clinical response in 2 weeks; at 6 weeks these eight developed tolerance, suggesting that L-tyrosine is not useful in attention deficit disorder, residual type.

(Am J Psychiatry 1987; 144:1071-1073)

A ttention deficit disorder, with a prevalence of 3%-10% (1), is probably the most common chronic psychiatric syndrome in children. Once generally believed to be a disorder that is outgrown in adolescence (2), it seems in many instances to continue into late adolescence and adult life (3, 4), in which case it is designated, according to DSM-III, as attention deficit disorder, residual type.

Although the etiology of these two conditions is unknown, a body of circumstantial evidence implicates abnormalities in phenethylaminergic or dopaminergic CNS functioning (5, 6). Since there is evidence that

pharmacological doses of dietary amino acids lead to increased brain levels of specific neurotransmitters (7), one approach that may elucidate the neurochemical bases of attention deficit disorder is to administer large quantities of precursor amino acids. Accordingly, we have conducted three clinical trials. In the first (5), L-dopa was found to be of no therapeutic benefit; however, a clear interpretation of the results was difficult because L-dopa in low doses produced nausea and sedation and therefore precluded a trial of higher, and possibly effective, doses. In the second trial (8), d,l-phenylalanine, a precursor of phenethylamine and catecholamines, produced a transient improvement in mood and a decrease in activity level but did not improve concentration; these results are also difficult to interpret. The third trial, which we describe in this paper, involved tyrosine. Tyrosine is the amino acid precursor for catecholamine synthesis, and its administration in pharmacological doses to animals can increase the rate of neuronal synthesis of dopamine and norepinephrine (7, 9). The fact that there have been reports of the therapeutic use of tyrosine in depression (9, 10) suggests that it is pharmacologically active in humans. A demonstration of L-tyrosine's efficacy in attention deficit disorder, residual type, would suggest that decreased dopaminergic or noradrenergic activity plays a role in the development of the disorder and that increased dopaminergic or noradrenergic activity plays a role in its improvement. This open study was therefore undertaken to investigate L-tyrosine's effect in patients with attention deficit disorder, residual type.

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#### **METHOD**

The proposal to conduct the experiment was submitted to and accepted by the University of Utah Human Experimentation Committee, and informed consent was obtained from each subject before voluntary entry into the experiment.

As a result of our previous studies, we revised the operational criteria, the Utah criteria, for attention deficit disorder, residual type. To meet these criteria, the subject must first have had a history of attention deficit disorder with hyperactivity in childhood, as well as both hyperactivity and attentional deficits as an adult. In addition, he or she must have had two of the following characteristics: 1) affective lability, 2) poor organization and an inability to complete tasks, 3) excessive or explosive temper, 4) impulsivity, and 5) low tolerance for stress. Subjects included in the study had never met DSM-III criteria for schizophrenia or schizoaffective disorder. In addition, they had no active major affective disorder and had none of the specific features of schizotypal disorder or borderline personality disorder.

No attempt was made to acquire a systematic sample. Referred patients who met the criteria for attention deficit disorder, residual type, were provisionally accepted if they were between 21 years old and 45 years old, had no medical contraindications to amino acid therapy, had no history of alcohol or substance abuse in the preceding 6 months, and, if female, were surgically sterile or were taking birth-control medication.

Placebo and L-tyrosine were prepared in identical-appearing capsules. Patients initially underwent a 1-week, single-blind placebo washout. Patients who did not show a moderate to marked improvement were then given an open 8-week trial of L-tyrosine. The amino acid was administered in three divided doses: 50 mg/kg of body weight per day, increased, as tolerated, to a maximum of 150 mg/kg of body weight per day.

Two measures were used to evaluate the patients' clinical status before the trial and at weekly intervals thereafter. 1) The Physician's Global Rating scale is a 7-point scale based on the physician's judgment of overall functioning: -3 = marked worsening, -2 = moderate worsening, -1=slight worsening, 0=no change, +1=mild improvement, +2=moderate improvement, and +3=marked improvement. 2) The targeted attention deficit disorder symptoms scale (unpublished) is divided into seven areas of dysfunction in attention deficit disorder, residual type: attentional difficulties, hyperactivity, temper problems, mood difficulties, impulsivity, overreactivity, and disorganization. Within each category are ordinal points with anchors provided for each, so that maximum dysfunction in each area would produce a total score of 40; the anchored scale is a modification of a measure still under development. Only the face validity of the latter scale has been established (4).

#### **RESULTS**

Sixteen subjects began the trial. One subject showed a moderate response during the single-blind trial of placebo, and three other subjects dropped out before the second week of the open trial (none of these three subjects, however, had complained of any side effects). The following data are derived from the 12 subjects (six women and six men) who completed an 8-week trial of tyrosine. Their mean±SD age was 30.2±7.5 years.

The dose of L-tyrosine was rapidly increased from 50 to 150 mg/kg per day with only minor side effects. In the initial phase, patients appeared to stabilize at 4 weeks, at which time, using the Physician's Global Rating scale, we saw marked improvement in two patients, moderate improvement in six, slight or no improvement in two, and slight worsening in two. Their mean ±SD target symptom scores during baseline (27.3±3.9) dropped by the end of the 8-week period  $(17.4\pm9.3)$ ; however, inspection of weekly target sympton ratings revealed that maximum improvement had occurred at the third or fourth week of treatment (best mean ±SD score=11.5±8.3). A repeated measures ANOVA examining baseline, best, and final target symptom scores was significant (F= 22.3, df=2, 22, p<.01), and a Newman-Keuls test for pairwise comparisons was applied. All three differences were statistically significant: baseline versus final (p<.01); baseline versus best (p<.01); and best versus final (p<.05). The analyses were consonant with our clinical observations: There were significant baseline to week 8 effects, but there was clinical regression between the subjects' best responses and their responses at 8 weeks. The condition of one subject was worsened by the treatment, and at 2 weeks the medication was discontinued. When he became progressively more angry and suspicious, his diagnosis was reconsidered and he was classified, after the fact, as having possible paranoid personality disorder.

#### CASE REPORT

Ms. A, a 35-year-old nurse and divorced mother of three, applied to our clinic for help with problems in concentration ("My mind wanders ... it is hard for me to keep my attention on one task and I am highly distractible"), disorganization, restlessness, poor organizational ability, irritability and bad temper, recurrent depression, and emotional overreactivity. Her memories of her childhood were sketchy, but she reported being a disciplinary problem. Her mother's responses to a questionnaire placed Ms. A in the 95th percentile of childhood "hyperactivity." Ms. A had had multiple therapeutic contacts: in college she had sought counseling because of difficulty in "coping"; at age 23 she received child guidance counseling; and after her divorce at age 25, she again sought counseling. Two years before her admission to our clinic, she had contacted the community mental health clinic for help with these and other problems and was given antidepressant medication, from which she did not benefit. Her marriage had been extremely stormy and terminated after 5 years with the birth of her third and last child. At the time she entered our program she was involved in a long-term relationship that had recently begun to unravel; she and her lover engaged in frequent arguments that were exacerbated by Ms. A's temper and the complaint that "problems just don't get solved." Both of her male children were "hyperactive," and she felt unable to manage them.

Ms. A showed no clinical improvement during the 1-week single-blind administration of placebo and was then given tyrosine. Two weeks after tyrosine treatment was initiated, she noted a substantial improvement in concentration, organization, restlessness, affective lability and "the blues," per, and handling of stress. Over the next 3-4 weeks the favorable response gradually disappeared, and she began to complain of nausea. By 8 weeks she showed no improvement whatsoever and was placed on d-amphetamine, which was gradually increased to 25 mg/day in divided doses. This regimen produced the same degree of control that had been seen with tyrosine. She was maintained on d-amphetamine until she and her lover moved away from Salt Lake City. During the 3 years of maintenance therapy, she showed no tolerance to d-amphetamine, and her work performance, her relationship with her children, and her relationship with her lover gradually improved.

#### **DISCUSSION**

Our first finding was that L-tyrosine was therapeutically effective after 2 or more weeks. This delay is similar to that found by Gelenberg et al. (9) in the tyrosine treatment of depression and to that encountered with the use of tricyclic antidepressants and monoamine oxidase inhibitors in the treatment of depression. The delay seen with antidepressants parallels changes in receptor function and suggests that analogous changes may have to occur before L-tyrosine becomes therapeutically effective. In our previous trials of d,l-phenylalanine (8), the pharmacological response was immediate, so we did not predict the

delay in L-tyrosine response; therefore, a placebo response is not likely, even in an open trial.

The second finding was that all the patients who responded to L-tyrosine became tolerant to its therapeutic effects. The clinical reports on the effects of L-tyrosine in depression (9, 10) do not discuss the length of time that the treatment remained effective or whether tolerance developed.

In conclusion, the three precursor studies—L-dopa (5), d,l-phenylalanine (8), and L-tyrosine—have not elucidated the putative functional defect in attention deficit disorder, residual type. Furthermore, none of these substances appears to have any clinical utility in the treatment of the disorder.

- Belmont L: Epidemiology, in Handbook of Minimal Brain Dysfunctions. Edited by Rie HE, Rie ED. New York, John Wiley & Sons, 1980
- 2. Laufer MW, Denhoff E: The hyperkinetic behavior syndrome in children. J Pediatr 1957; 50:463-473
- 3. Weiss G: Followup studies on outcome of hyperactive children. Psychopharmacol Bull 1985; 21:169–177
- Wender PH, Reimherr FW, Wood D, et al: A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. Am J Psychiatry 1985; 142: 547-552
- Wood D, Reimherr F, Wender PH: Effects of levodopa on attention deficit disorder, residual type. Psychiatry Res 1982; 6: 13-20
- 6. Wender PH, Wood DR, Reimherr FW, et al: An open trial of pargyline in the treatment of attention deficit disorder, residual type. Psychiatry Res 1983; 9:329-336
- Wurtman RJ, Fernstrom JD: Control of brain neurotransmitter synthesis by precursor availability. Biochem Pharmacol 1976; 25:1691-1696
- 8. Wood DR, Reimherr FW, Wender PH: The treatment of attention deficit disorder with *d,l*-phenylalanine. Psychiatry Res 1985; 16:21–26
- 9. Gelenberg AJ, Wojcik JD, Growdon JH, et al: Tyrosine for the treatment of depression. Am J Psychiatry 1980; 137:622-623
- 10. Goldberg IK: L-Tyrosine in depression (letter). Lancet 1980; 2: 364-365

### Mental Health Effects of the Three Mile Island Nuclear Reactor Restart

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Controversy over potential mental health effects of the Three Mile Island Unit-1 restart led the authors to examine prospectively the pattern of psychiatric symptoms in a sample of Three Mile Island area mothers of young children. Symptom levels after restart were elevated over previous levels; a sizable subcohort of the sample reported relatively serious degrees of postrestart distress. History of diagnosable major depression and generalized anxiety following the Three Mile Island accident, plus symptoms and beliefs about personal risk prior to the restart, best predicted postrestart symptoms.

(Am J Psychiatry 1987; 144:1074–1077)

A dramatic and immediate consequence of the 1979 Three Mile Island accident was its deleterious effect on local residents' mental health (1–3). Like many natural and technological disasters, the accident was not an acute, time-limited event. Rather, it entailed a sequence of interrelated events that unfolded over several years, thereby creating a situation of chronic stress (4, 5). During this period, one major controversy focused on whether restarting the undamaged Unit-1 reactor constituted an environmental hazard to mental health (6). After an extended legal battle that eventually reached the U.S. Supreme Court, the reactor was restarted in October 1985.

The present research examined prospectively the psychiatric effects of the restart on a representative sample of mothers of young children living in Three Mile Island area communities. This cohort was deemed at high risk for two reasons. First, in comparison with other local residents, mothers experienced

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elevated levels of psychiatric symptoms and diagnosable major depression and generalized anxiety following the 1979 accident (1). Second, these mothers consistently viewed the Three Mile Island situation as one of danger and personal risk during the interim between the accident and the restart (7). Research on the behavioral effects of beliefs suggests that the extremity and temporal stability of their views should elevate their distress levels following additional Three Mile Island-related events, such as the restart (8).

We focused, then, on whether psychiatric symptoms following the restart increased over previous levels. In addition, previous life events and disaster research (9, 10) led us to hypothesize that two classes of variables would be important predictors of distress levels after the restart for this cohort: 1) psychiatric status prior to and immediately following the original 1979 accident and residential status at those times, and 2) psychosocial variables reflecting beliefs about personal risks and social support and coping strategies during the years subsequent to the accident.

#### **METHOD**

A panel of 385 women living near Three Mile Island were interviewed in their homes in fall 1981 and fall 1982 during an investigation of Three Mile Island's long-term mental health effects (1, 11). All had delivered a child between January 1978 and March 1979, the month the accident occurred. Since Pennsylvania law prohibited access to vital statistics records, subjects were drawn from area newspaper birth announcements. Hospitals routinely reported birth data to newspapers, and virtually all local women delivered in a hospital, thereby minimizing sample bias.

Of these 385 subjects, 199 returned a follow-up questionnaire mailed during the month after the Unit-1 reactor restart (fall 1985). The nonresponse rate of 48.3% most likely was due to our inability to conduct personal interviews in 1985, in view of the fact that attrition between the two interviews before the restart (during the period of study funding) was only 6%. This explanation is supported by our finding that 1985 follow-up respondents were very similar to 1985 nonrespondents on both demographic characteristics prior

TABLE 1. Characteristics Before Restart of Nuclear Reactor of Mothers in Three Mile Island Area<sup>a</sup> Who Did (N=199) or Did Not (N=186) Respond to Questionnaire Following Reactor Restart

	Respor	ıdents	Nonrespondents		
Variable	N	%	N	%	
Education beyond high school	111	56	88	47	
Income over \$20,000	130	65	114	61	
Three or more children	53	27	59	32	
Full- or part-time employment	88	44	88	47	
Married	194	97	182	98	
Age less than 35 years	181	91	162	87	
Caucasian	192	96	180	97	
Clinical psychiatric disorder					
Before accident	40	20	32	17	
After accident	36	18	34	18	
Evacuated after accident	174	87	165	89	

<sup>&</sup>lt;sup>a</sup>Mean±SD distances from Three Mile Island for the respondents and nonrespondents were 6.66±2.84 and 6.50±3.17 miles, respectively.

to the restart and prerestart psychiatric and psychosocial measures (see also tables 1 and 2).

Psychiatric symptoms following the restart were assessed with the depression, anxiety, and hostility subscales of the Symptom Checklist-90 (SCL-90) (12), a scale measuring current subclinical levels of disturbance. A summary symptom index was created by averaging the items (0=not at all, 4=extremely distressed). This index was log-transformed prior to analyses to reduce skewness in its distribution.

A complete demographic profile was obtained at the initial (1981) interview. For multivariate analyses, we focused on four characteristics on which the women varied substantially: education, income, number of children, and employment status.

At the initial interview we determined 1) whether subjects had experienced major depression and/or generalized anxiety at any time prior to the 1979 accident (diagnosed with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version [13], using Research Diagnostic Criteria [14]), 2) whether subjects experienced major depression and/or generalized anxiety during the 18 months after the accident, 3) residential distance from the plant when the accident occurred, and 4) whether subjects evacuated the area.

Several variables reflecting current psychosocial status at the 1981 and 1982 interviews were assessed: 1) subclinical psychiatric symptoms (using the SCL-90 items described above, averaged and log-transformed for multivariate analyses), 2) beliefs about personal risk (average of four items dealing with perceptions of the safety of living near Three Mile Island and fears about future health risks [7]), 3) availability and quality of social support from friends (assessed with scales adapted from Moos [15]), and 4) coping style (assessed with the Mastery scale [16]). For multivariate analyses, an average prerestart score was created for each of these psychosocial variables, since they were stable across the 1981 and 1982 interviews (median r=.51).

Tables 1 and 2 present descriptive statistics for all predictors.

#### RESULTS

We first examined whether symptom levels following restart increased over previous levels. A one-way repeated measures analysis of variance indicated that subclinical symptoms changed over time (F=12.60, df=2, 396, p<.001); a planned contrast showed that symptom levels were significantly higher after restart (untransformed mean=.591) than before (untransformed mean=.473 and .424 for the first and second interviews, respectively; F=86.86, df=1, 396, p<.001; r=.42). Among a subsample of 134 of the 199 women who had also been interviewed 9 months after the 1979 accident (1), symptom levels were slightly higher after restart than they had been in 1979 (mean=.581 and .514, respectively).

From an epidemiologic perspective, one would expect approximately 16% of the sample to score above one standard deviation from the mean for a normative community sample of women (12). Indeed, prior to the restart, the scores of 13% (N=26), 15% (N=30), and 21% (N=42) of the sample exceeded one standard deviation on the depression, anxiety, and hostility subscales, respectively. After the restart, however, the percentages scoring above one standard deviation on these subscales increased substantially to 21% (N=41), 25% (N=49), and 36% (N=72), respectively.

Our second question concerned whether responses prior to the restart would predict which women would show relatively more postrestart distress. Table 3 presents correlations among demographic variables, variables related to the original accident, subsequent psychosocial variables reflecting subjects' 1981–1982 status, and 1985 postrestart symptoms. The majority of hypothesized predictors correlated significantly with postrestart symptoms in the expected direction. Symptom levels following the restart were also regressed on the predictors in order to examine each predictor's direct, unique impact; higher prerestart symptom levels and prior beliefs of greater personal risk most strongly predicted elevated postrestart symptom levels (see table 3). No significant interactions between predictors were found.

In addition to any direct effects on symptoms after restart, episodes of clinical disorder occurring prior to and during the 18-month interval after the 1979 accident conceivably influenced postrestart symptoms indirectly. That is, they may have affected 1981–1982 symptoms and beliefs about personal risk, the two variables that in turn were the most important predictors of postrestart distress. To examine this possibility, the 1981–1982 prerestart symptom and belief measures were each regressed on the measures of pre-1979 and 1979 clinical status. We found that clinical disorder during the 18 months following the accident significantly predicted both prerestart variables (symp-

TABLE 2. Psychosocial Status Before Restart of Nuclear Reactor of Mothers in Three Mile Island Area Who Did (N=199) or Did Not (N=186) Respond to Questionnaire Following Reactor Restart

Measure <sup>a</sup>	Respor	ndents	Nonrespondents		
	Mean	SD	Mean	SD	
Symptoms (0=less, 4=more distress)	0.45	0.39	0.44	0.42	
Beliefs of personal risk (1=less, 4=more)	2.85	0.85	2.88	0.85	
Social support quality (0=less, 3=more)	1.77	0.45	1.84	0.47	
Social support availability (0=less, 4=more)	3.65	0.52	3.60	0.53	
Coping (1=less, 5=greater sense of mastery over events)	2.17	0.39	2.16	0.35	

<sup>&</sup>lt;sup>a</sup>Averaged over 1981 and 1982 assessments.

TABLE 3. Correlations and Standardized Regression Coefficients for Major Study Variables in 199 Mothers in Three Mile Island Area

					Co	orrelatio	on (r)						Follo Rest Nu	otoms owing art of clear actor
Variable .	1	2	3	4	5	6	7	8	9	10	11	12	r	b <sup>a</sup>
Demographic measures 1. Education 2. Income 3. Number of children 4. Employment status Clinical and residential status before and after accident	.31 <sup>b</sup> 07 .19 <sup>c</sup>	.10 .21°	22 <sup>c</sup>										02 27 <sup>b</sup> 02 03	.10 16 <sup>c</sup> .01 .00
<ul><li>5. Preaccident disorder</li><li>6. Postaccident disorder</li><li>7. Miles from Three Mile Island</li><li>8. Evacuated</li><li>Psychosocial status before restart</li></ul>	.06 03 .06 .02	01 .00 .05 03	.04 06 11 .00	17 <sup>c</sup> .13 .04 .09	.32 <sup>b</sup> .04 .11	.00 .10	29 <sup>b</sup>						.10 .20° 16° .16°	.00 .08 15° .03
of nuclear reactor <sup>d</sup> 9. Symptoms 10. Personal risk beliefs 11. Social support quality 12. Support availability 13. Coping	02 13 03 .04 .24 <sup>b</sup>	22° 10 02 .11 .21°	.02 10 .12 .10 02	07 .06 .00 .02 .07	.18 <sup>c</sup> 04 .01 .03 .04	.17° .20° .02 .02 23°	04 .09 09 03 02	.13 .11 .07 .01	.15° 17° 12 35°	.02 .00 05	.32 <sup>b</sup> .13	.20°	.52 <sup>b</sup> .30 <sup>b</sup> 08 20 <sup>c</sup> 24 <sup>b</sup>	.41 <sup>b</sup> .23 <sup>b</sup> .02 14 <sup>c</sup> 03

 $<sup>^{</sup>a}R=.63.$ 

toms before restart: b=.16, p<.05; beliefs before restart: b=.16, p<.05). Thus, women with diagnosable episodes of disorder immediately after the accident were more likely to report subsequently higher symptom levels and beliefs of greater personal risk prior to the restart. These latter two factors, in turn, directly predicted higher symptom levels following the restart. Figure 1 depicts the nature of these mediated effects.

#### DISCUSSION

Our findings suggest that the 1985 restart of the undamaged Three Mile Island reactor elevated levels of psychiatric symptoms among mothers of young children. This interpretation is strengthened by our design, which assembled baseline data prospectively rather than retrospectively. It is unlikely that our

results are biased by the 48.3% attrition rate among subjects who had participated in earlier waves of data collection; respondents were very similar to nonrespondents on the demographic, clinical, and psychosocial variables measured previously. Nevertheless, it is important to note that respondents and nonrespondents may have differed on other variables not assessed.

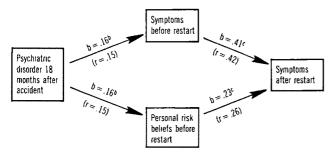
What clinical and policy implications are contained in our data? In keeping with critiques of earlier research on environmental hazards (17, 18), we emphasize the need to examine psychosocial risk factors when assessing the mental health effects of environmental stressors. With regard to etiologic mechanisms, our data indicate that a mother's initial pattern of responding to the Three Mile Island accident not only directly influenced levels of postrestart symptoms but exerted mediated effects as well. Thus, a history of major depression and/or generalized anxiety in the 18 months following the accident led to subsequently

<sup>&</sup>lt;sup>b</sup>p<.001.

 $c_{p}^{2} < .05$ .

dSee table 2 for direction in which each variable was scored.

FIGURE 1. Standardized Regression Coefficients and Partial Correlations<sup>a</sup> Illustrating Mediated Effects of Diagnosable Disorder on Postrestart Symptoms for 199 Mothers in the Three Mile Island



<sup>a</sup>Partial correlations (in parentheses) indicate the size of each predictor-outcome association, controlling for other predictors. See text for description of complete regression equations.

<sup>c</sup>p<.001.

higher symptom levels before the restart and stronger beliefs of greater personal risk. These responses, in turn, were directly associated with elevated postrestart distress.

In terms of potential policy implications, our findings highlight the need to specify intervention strategies for not only the short-term but also the long-term sequelae of technological disasters. Although procedures for coping with the former have been refined to relatively sophisticated levels (19), far less progress is evident in designing interventions for the extended deleterious consequences of accidents such as that at Three Mile Island. The recent Soviet nuclear accident at Chernobyl dramatizes the international scope of this problem and the significance of resolving it. Our findings suggest that identification of high-risk cohorts, e.g., persons exhibiting chronic as well as acute maladjustment patterns in a disaster's aftermath, is a useful approach to targeting scarce psychiatric resources when additional environmental stresses are anticipated.

#### REFERENCES

1. Bromet EJ, Parkinson DK, Schulberg HC, et al: Mental health of residents near the Three Mile Island reactor: a comparative study of selected groups. J Preventive Psychiatry 1982; 1:225-276

- 2. Dohrenwend BP, Dohrenwend BS, Kasl SB, et al: Technical Staff Analysis Report on Behavioral Effects to the President's Commission on the Accident at Three Mile Island. Washington, DC, US Government Printing Office, October 31, 1979
- 3. Houts PS, Miller RW, Tokuhata GK, et al: Health-Related Behavioral Impact of the Three Mile Island Nuclear Incident, Parts I, II, III. Harrisburg, Pennsylvania Department of Health,
- 4. Fried M: Endemic stress: the psychology of resignation and the politics of scarcity. Am J Orthopsychiatry 1982; 52:4-19
- 5. Shore JH, Tatum EL, Vollmer WM: Psychiatric reactions to disaster: the Mount St Helens experience. Am J Psychiatry 1986; 143:590–595
- 6. Hartsough DM, Savitsky JC: Three Mile Island: psychology and environmental policy at a crossroads. Am Psychol 1984; 39:1113-1122
- 7. Dew MA, Bromet EJ, Schulberg HC: Application of a temporal persistence model to community residents' long-term beliefs about the Three Mile Island nuclear accident. J Applied Social Psychol (in press)
- 8. Schwartz SH: Temporal instability as a moderator of the attitude-behavior relationship. J Pers Soc Psychol 1978; 36: 715-724
- 9. Dohrenwend BP: Life stress and illness: formulation of the issues, in Stressful Life Events and Their Contexts. Edited by Dohrenwend BS, Dohrenwend BP. New York, Prodist, 1981
- 10. Janis I: The psychological effects of warning, in Man and Society in Disaster. Edited by Baker G, Chapman D. New York, Basic Books, 1962
- 11. Dew MA, Bromet EJ, Schulberg HC: A comparative analysis of two community stressors' long-term mental health effects. Am J Community Psychol 1987; 15:167-184
- 12. Derogatis LR: The SCL-90 Manual I: Scoring, Administration and Procedures for the SCL-90. Baltimore, Johns Hopkins University School of Medicine, Clinical Psychometrics Unit,
- 13. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
- 14. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773-
- 15. Moos R: Evaluating Correctional and Community Settings. New York, John Wiley & Sons, 1975
- 16. Pearlin LI, Schooler C: The structure of coping. J Health Soc Beh 1978; 19:2-21
- 17. Green B: Assessing levels of psychological impairment following disaster: consideration of actual and methodological dimensions. J Nerv Ment Dis 1982; 170:544-552
- 18. Shore JH, Tatum EL, Vollmer WM: Evaluation of mental health effects of disaster, Mount St Helens eruption. Am J Public Health 1986; 76(March suppl):76-83
- Cohen R, Ahearn F: Handbook for Mental Health Care of Disaster Victims. Baltimore, Johns Hopkins University Press,

<sup>&</sup>lt;sup>b</sup>p<.05.

### Clinical and Research Reports

### Effect of Pregnancy on Panic Attacks

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Three women with panic disorder showed marked improvement in their panic symptoms during pregnancy. Such effects might be due to pregnancy's blunting of the sympathoadrenal response to simple physiologic stimuli, effects on barbiturate receptors, or improvement in psychological functioning.

(Am J Psychiatry 1987; 144:1078–1079)

P anic disorder has a prevalence of 1% to 2% in the general population and affects more females than males (1). The etiology of panic attacks remains unclear, although various theories, including alterations in neurotransmitter systems, have been postulated (2, 3). The relationship between the menstrual cycle and/or pregnancy and the frequency and intensity of panic attacks has not been explored, to our knowledge. In this report we describe three women who met the DSM-III criteria for panic disorder and experienced improvement in their panic symptoms during pregnancy.

#### CASE REPORTS

Case 1. Ms. A, a 33-year-old woman, had had "panic feelings" since adolescence. At age 23, while in a department store, she experienced her first major panic attack, which was characterized by palpitations, nausea, tremors, dyspnea, and an overwhelming sense of being "out of control." Within several months of this episode daily panic attacks developed and she began to avoid people and shopping malls. With the onset of pregnancy at age 25, she experienced a dramatic reduction in panic symptoms, which continued until delivery. For the next 3 years she experienced

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frequent panic attacks and extensive avoidance behavior, including limitation of driving. During her second pregnancy, at age 29, she felt "instantaneously better," had feelings of "more control over life," and was able to drive much farther from home. After delivery she required antidepressants to control her panic symptoms, and she still "looked for exits" when in confined spaces. At the time of the interview she was 5 months into her third pregnancy and was free of medication. As in her previous pregnancies, she was experiencing no panic attacks and was less socially inhibited.

Case 2. Ms. B, a 49-year-old woman, had experienced her first panic attack at age 22 after her sister's wedding. Thereafter, feelings of unreality and extreme fear occurred regularly along with hyperventilation, palpitations, and stomach discomfort. Concurrent with the onset of her panic attacks were extreme phobias of height, driving a car, and eating food out of cans. After she became pregnant at age 24, she was able to drive long distances from home and look out of tall buildings without fear; the severity and frequency of her panic attacks also markedly lessened. After delivery she experienced a return of depression accompanied by anxious feelings, and within 1 week she was again having frequent panic attacks. These attacks persisted for the next 6 months, until she again had relief from her symptoms during her second pregnancy. After delivery she experienced an exacerbation of panic symptoms for years, until she obtained medical treatment. In retrospect, she stated that "my pregnancies were the best periods of my life" from the standpoint of emotional well-being.

Case 3. Ms. C, a 57-year-old woman, had experienced her first discrete episode of panic at age 30, between her third and fourth pregnancies. Her panic occurred fairly regularly once or twice a month and typically included palpitations, trembling of her whole body, and dyspnea, as well as "feelings of terror" and "total helplessness." During the first few weeks of her fourth pregnancy (2 years after her panic first began) she noted a rapid reduction in the frequency and severity of her panic symptoms, and by the end of her first trimester she was panic free. She described the gravid state as providing her with a previously unknown "level of protection" which enabled her to function effectively amid crowds and instilled in her a new sense of confidence that everything

would work out. In addition, she felt happier than usual and close to people and had higher self-esteem. She noted that during this pregnancy she did have intermittent periods of anxiety yet had no feelings of panic or somatic symptoms associated with it.

Two months after childbirth Ms. C again began to experience panic attacks at her previous frequency. These continued uninterrupted for 3 years, when she became pregnant for the fifth time and experienced an identical pattern of freedom from panic. After that pregnancy Ms. C had over 20 years of increasingly severe panic episodes which occurred at least once a week without interruption, except for 6 months when she was taking a monoamine oxidase inhibitor. During the 2 years before her last pregnancy Ms. C had taken birth control pills and noticed no change in the frequency of panic episodes and no clear association of panic with her menstrual periods.

#### DISCUSSION

These women with a diagnosis of panic disorder illustrate an interesting relationship between pregnancy and symptoms of panic. In each case there was a marked attenuation in the severity and frequency of panic during pregnancy that was not identifiable in the nongravid state. Since the improvement was not attributable to medication, psychotherapy, or stabilization of life situations, it raises the possibility that pregnancy itself might have an antipanic effect.

Understanding the mechanism whereby pregnancy might improve panic is complicated by the complex and multiple physiological changes that occur in pregnancy. Many of these changes, such as increases in the basal metabolic rate and the minute ventilation (with a decrease in partial CO<sub>2</sub> pressure) (4), might be expected to be anxiogenic if, as has been suggested (5), panic patients are more sensitive to altered bodily sensations.

There seem to be at least three possible explanations for our observations. The first is that pregnancy stabilizes and blunts the sympathoadrenal response to a variety of simple physiologic stimuli. In particular, controlled studies (6, 7) have revealed an attenuation in both heart rate and release of norepinephrine in response to postural changes and isometric exercise. Recent reports by two separate groups (8, 9) have suggested greater lability of noradrenergic control of sympathetic nervous system function in panic disorder. Thus, the physiological changes in pregnancy would tend to oppose this and might prevent the paroxysmal activity of sympathetic function seen during a panic attack.

The second possibility is that the hormonal changes in pregnancy may exert an anxiolytic effect by means of interactions with barbiturate receptors. Recently it has been demonstrated (10) that certain steroid derivatives, including progesterone metabolites, possess barbiturate-like activity. Since some barbiturates are effective anxiolytics that have been used to treat anxiety disorders, it is possible that naturally occurring derivatives could ameliorate panic disorder.

Finally, the cognitive and psychological effects of pregnancy should not be overlooked. The sense of purpose and self-esteem that planned pregnancy may bring could improve psychological function.

We have described three women who experienced improvement of their panic symptoms during pregnancy. Although this observation could be an artifact of the episodic nature of panic attacks, we feel this is unlikely since the subjects described dramatic improvement in their symptoms during each pregnancy but no similar episodes when they were not pregnant. If this finding is substantiated in a larger number of panic disorder patients, it could have implications for the therapeutic management of young women taking medication for panic disorder who wish to become pregnant and for research aimed at understanding the etiology of panic.

#### REFERENCES

- Robins LN, Helzer JE, Weissman MM, et al: Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984; 41:949–958
- Klein DF: Anxiety reconceptualized, in Anxiety: New Research and Changing Concepts. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
- Carr DB, Sheehan DV: Panic anxiety: a new biological model. J Clin Psychiatry 1984; 45:323–330
- Guyton AC (ed): Textbook of Medical Physiology. Philadelphia, WB Saunders, 1981
- 5. Clark DM: A cognitive approach to panic. Behav Res Ther 1986; 24:461–470
- Barron WM, Mujais SK, Zinaman M, et al: Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. Am J Obstet Gynecol 1986; 154:80–84
- Nisell H, Hjemdahl P, Linde B, et al: Sympathoadrenal and cardiovascular reactivity in pregnancy-induced hypertension, II: responses to tilting. Am J Obstet Gynecol 1985; 152:554–560
- 8. Charney DS, Heninger GR: Abnormal regulation of noradrenergic function in panic disorders: effects of clonidine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 1986; 43:1042–1054
- Nutt DJ: Increased central alpha 2-adrenoceptor sensitivity in panic disorder. Psychopharmacology (Berlin) 1986; 90:268– 269
- Majewska MD, Harrison NL, Schwartz RD, et al: Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986; 232:1004–1007

### CO<sub>2</sub> Challenge of Patients With Panic Disorder

Minna R. Fyer, M.D., Judy Uy, M.D., Jose Martinez, B.S., Raymond Goetz, Ph.D., Donald F. Klein, M.D., Abby Fyer, M.D., Michael R. Liebowitz, M.D., and Jack Gorman, M.D.

In an open trial, five of eight panic disorder patients and none of five control subjects panicked after inhalation of two breaths of 35%  $CO_2$  and 65%  $O_2$ ; none panicked after placebo. Using 35%  $CO_2$  to induce panic is safe, simple, and well tolerated and may provide a valuable laboratory model of panic.

(Am J Psychiatry 1987; 144:1080–1082)

There is now evidence that CO<sub>2</sub> inhalation is anxiogenic and that patients with panic disorder have heightened sensitivity to CO<sub>2</sub>. Several investigators (1–3) have reported that continuous inhalation of low concentrations (4%–8%) of CO<sub>2</sub> provokes panic in panic disorder patients but not in normal subjects.

Using a different approach, Griez and van den Hout (4) attempted to provoke panic with single- and double-breath inhalation of a mixture of 35% CO<sub>2</sub> and 65% O<sub>2</sub>. Although patients and normal subjects experienced autonomic anxiety symptoms, only panic disorder patients reported "high degrees of subjective anxiety."

If inhalation of 35% CO<sub>2</sub> and 65% O<sub>2</sub> is panicogenic in patients with a history of spontaneous panic but not in normal subjects or patients with other anxiety disorders, it would provide a valuable laboratory model for the study of panic. It has also been hypothesized (5) that CO<sub>2</sub> hypersensitivity is directly involved in the etiological mechanism of panic. If so, study of CO<sub>2</sub>-induced panic might bring us closer to understanding the pathophysiology of panic. We report an open pilot study of double-breath inhalation of 35% CO<sub>2</sub> and 65% O<sub>2</sub> in patients with *DSM-III* panic

disorder or agoraphobia with panic attacks and in normal control subjects.

#### **METHOD**

Eight patients with DSM-III panic disorder or agoraphobia with panic attacks (mean±SD age = 36±6.8 years) and five normal volunteers (mean±SD age = 29.4±1.7 years) participated in this study. The difference in age between groups was significant (t=2.24, p<.05), but there were no significant differences between groups in height or weight. All patients were tested before receiving treatment; all patients and control subjects were in excellent health and had been medication free for at least 2 weeks. All subjects arrived at the Biological Studies Unit after a 12-hour abstinence from caffeine-containing beverages and nicotine. Written informed consent was obtained.

All subjects were seated and informed that they would be inhaling compressed air (placebo) and CO<sub>2</sub> and that these gases are not harmful but might induce anxiety or a panic attack. They then practiced the method of inhalation as follows: the subject exhales as fully as possible and then places the mask on his or her face, takes as fast and deep a breath as possible, and holds it for 5 seconds. The sequence is then repeated.

After being at rest for 20 minutes, each subject inhaled two breaths of placebo. After a second period of rest, each inhaled two breaths of 35% CO<sub>2</sub> and 65% O<sub>2</sub>. Three subjects (one control and two panic disorder) were given the gases in reverse order. The subjects were blind to the order of the gases. Because this was a preliminary trial, the investigators were not blind to patient diagnosis or order of the gases.

The decision to call a response a panic attack was based on the investigator's observations and the subject's report. Our definition of panic requires not only fulfillment of *DSM-III* criteria but also a subjective sense of terror, impending doom, or desire to flee, as well as a report by the patient that CO<sub>2</sub>-induced panic closely resembles spontaneous panic.

We measured anxiety with the Acute Panic Inventory, a 17-item questionnaire that measures the severity of the usual symptoms of an acute panic attack on a scale of 0 (absent) to 3 (severe), and an anxiety self-rating scale, which rates overall anxiety level from

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TABLE 1. Repeated Measures ANOVA Comparison of Anxiety Responses of Five Panickers and Five Control Subjects to 35% CO2 and Placebo

Comparison	Acute Panic Inve	entory Scores <sup>a</sup>	Anxiety Self-Rating Scale Scoresb		
	F (df=1, 8)	p	F (df=1, 7)	p	
Main Effects					
Diagnosis <sup>c</sup>	24.07	<.001	118.86	<.0002	
Condition <sup>d</sup>	6.32	<.036	9.04	<.020	
Time <sup>e</sup>	14.00	<.006	17.43	<.004	
Interactions					
Condition by Diagnosis			5.33	<.054	
Time by Diagnosis	<u></u>		11.67	<.011	
Condition by Time	34.22	<.0004	38.11	<.0005	
Condition by Time by Diagnosis	9.02	<.017	38.11	<.033	

<sup>&</sup>lt;sup>a</sup>Five panickers and five control subjects.

0 (least) to 10 (most ever experienced). Ratings were obtained immediately before and after inhalation of each gas. In addition, before the procedure, the eight patients were asked to retrospectively rate themselves on the Acute Panic Inventory for a typical (for them) panic attack.

A Fisher's exact test was used to compare the rate of 35% CO<sub>2</sub>-induced panic in the control and patient groups. Because we had predicted, on the basis of previous work, that CO<sub>2</sub> would induce panic, a one-tailed test was used. In all other cases, two-tailed tests were used. To determine whether the anxiety responses to 35% CO<sub>2</sub> challenge of panicking patients differed from those of control subjects, we compared the scores from both anxiety measures using a 2×2×2 (panickers versus control subjects, CO<sub>2</sub> versus placebo, and pre- versus postinhalation) repeated-measures analysis of variance (ANOVA).

#### **RESULTS**

Five (63%) of the eight panic disorder patients and none of the five normal control subjects experienced panic attacks with 35% CO<sub>2</sub> and 65% O<sub>2</sub> inhalation (Fisher's exact test, p <.04, one-tailed). Two additional patients described "prepanic" feelings—that is, they felt as if an attack were beginning but never fully developed. Although they met four of the 12 DSM-III criteria for a panic attack, they were not considered panickers because the symptoms were fleeting and a subjective sense of terror was not established.

The control subjects experienced very mild anxiety and some somatic symptoms with CO<sub>2</sub> inhalation. These symptoms did not resemble panic. None of the subjects panicked in response to placebo. One control subject experienced mild anxiety with placebo; none of the panickers experienced any increase in anxiety.

All five panickers described CO<sub>2</sub>-induced panic as very similar to their naturally occurring panic. There was no difference between the panickers' mean±SD Acute Panic Inventory scores during 35% CO<sub>2</sub>-in-

duced panic and those from their retrospective rating of a typical, spontaneous panic  $(24.6\pm6.5 \text{ and } 28.0\pm10.2, \text{ respectively}).$ 

When we compared the Acute Panic Inventory scores of panickers and control subjects (table 1), we found a significant Condition by Time by Diagnosis interaction, indicating that panickers reacted more markedly to CO<sub>2</sub> than did control subjects. This same interaction was found when we compared the anxiety self-rating scale scores of the panickers and control subjects, indicating that panic disorder patients who panicked in response to 35% CO<sub>2</sub> reacted more markedly to CO<sub>2</sub> than to placebo and more markedly to CO<sub>2</sub> than did control subjects. A difference in baseline level for anxiety did not account for these findings.

#### **DISCUSSION**

This study suggests that double-breath inhalation of 35% CO<sub>2</sub> and 65% O<sub>2</sub> provokes panic attacks in panic disorder patients but not in normal control subjects. The panic provoked by 35% CO<sub>2</sub> appears to closely resemble patients' naturally occurring panic. This finding is in agreement with those of previous investigators (1–4).

Although these results must be viewed with caution because of the small number of subjects and the absence of double-blind procedures, they are consistent with the hypothesis (5) that panic disorder patients have abnormally sensitive CO<sub>2</sub> receptors. When challenged with increased concentrations of CO<sub>2</sub>, these receptors are triggered and an extreme ventilatory response leading to panic ensues. The ability of 35% CO<sub>2</sub> to quickly induce panic raises the possibility that panic disorder patients have both peripheral and central hypersensitivity to CO<sub>2</sub>.

This procedure is safe and simple, as long as only two breaths of CO<sub>2</sub> are permitted. If panic after inhalation of 35% CO<sub>2</sub> proves to be specific to patients with a history of spontaneous panic, this procedure will provide a valuable laboratory model for the

bFive panickers and four control subjects.

<sup>&</sup>lt;sup>c</sup>Panickers versus control subjects.

dCO2 versus placebo (air).

<sup>&</sup>lt;sup>e</sup>Pre- versus postinhalation.

study of panic. If it can be made sufficiently sensitive, it may ultimately prove useful as an office-based diagnostic procedure in the evaluation of many patients with pathological anxiety.

#### REFERENCES

- Cohen ME, White PD: Life situations, emotions and neurocirculatory asthenia. Psychosom Med 1951; 13:335–357
- 2. Gorman JM, Askanazi J, Liebowitz MR, et al: Response to

- hyperventilation in a group of patients with panic disorder. Am J Psychiatry 1984; 41:857-861
- 3. Woods SW, Charney DS, Lake J, et al: Carbon dioxide sensitivity in panic anxiety: ventilatory and anxiogenic response to carbon dioxide in healthy subjects and panic anxiety patients before and after alprazolam treatment. Arch Gen Psychiatry 1986; 43:900–910
- Griez E, van den Hout M: Panic symptoms after inhalation of carbon dioxide. Br J Psychiatry 1984; 144:503–507
- Gorman JM, Liebowitz MR, Fyer AJ, et al: Possible respiratory abnormalities in panic disorder. Psychopharmacol Bull 1986; 22:797-801

# Lorazepam for Psychogenic Catatonia

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Catatonia poses special diagnostic and management problems for the psychiatrist. The authors report three patients with psychogenic catatonia who received intramuscular lorazepam and experienced rapid resolution of their conditions. (Am J Psychiatry 1987; 144:1082–1083)

L orazepam is a benzodiazepine with an intermediate-length effect and a half-life of 10-20 hours. It is the only benzodiazepine with proven bioavailability after intramuscular injection (1). Fricchione et al. (2) reported its effectiveness in reversing neuroleptic-induced catatonia. Many reports (1-3) indicate its effectiveness in reducing akathisias, extrapyramidal symptoms, and agitated states and as an anesthetic, anticonvulsant, anxiolytic, and hypnotic agent. As a facilitator of the  $\gamma$ -aminobutyric acid (GABA) system, lorazepam is thought to act both in the limbic system and in certain layers of the cerebral cortex (3).

Catatonia is a cluster of marked psychomotor disturbances of various etiologies. There are excited and retarded types, but we will focus on the the latter. Morrison (4) studied 250 cases of retarded catatonia and identified five major clinical signs: mutism, rigidity, negativism, posturing, and staring into space.

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Fricchione et al. (2, 5) suggested a physiologic similarity between neuroleptic-induced catatonia and psychogenic catatonia. They felt that neuroleptic malignant syndrome and lethal catatonia result from progression of those respective states. The following cases indicate a possible link between psychogenic catatonia and GABA systems.

#### CASE REPORTS

Case 1. Mr. A, a 67-year-old man, was admitted to a hospital department of medicine in an unarousable state. The results of physical and laboratory examinations and an ECG were normal. His blood alcohol level was zero, and a urine screen showed amitriptyline. There were no signs of antidepressant toxicity. There were no identifiable neurological deficits, but Mr. A had exhibited waxy flexibility in the emergency room. The results of an EEG and CAT scan were normal. Mr. A remained mute and unresponsive for 3 days, at which point the psychiatry department was consulted. Mr. A was found lying in bed with his eyes shut, unresponsive to questions, and attempts to open his eyes were met with resistance. No waxy flexibility was noted; however, when his arm was elevated above his forehead and released, it fell to his side. A diagnosis of conversion disorder appearing as a catatonic stupor was made. He was given 2 mg of intramuscular lorazepam, and within half an hour he was able to converse. He reported having "sex with a local girl" before admission and complained of impotency and a penile rash of recent onset. His past history indicated an episode of "brief reactive psychosis." Amitriptyline had been prescribed for back pain 2 years previously. The results of a mental status examination were unremarkable. The following day Mr. A had a recurrence of catatonic stupor; he received a second

dose of lorazepam, and the results were similar. He was maintained on oral lorazepam. A thorough evaluation for impotency revealed inhibited sexual excitement, which was the final diagnosis. Eight months later, Mr. A had made significant improvement and had had no relapses.

Case 2. Mr. B, a 63-year-old man, was admitted for evaluation of muteness, anorexia, and immobility. He had undergone a right craniotomy for removal of a parietal meningioma 18 months earlier. Physical examination revealed a villous adenoma of the rectum, for which Mr. B had earlier refused surgery. The results of laboratory examinations, an EEG, and a CAT scan were normal. The neurology consultant could find no basis for this behavior. The psychiatrist found Mr. B to be mute, staring about, and apparently ignoring the presence of the interviewer. No waxy flexibility was noted, and he did not resist examination. Family members reported similar behavior 6 years earlier after Mr. B had lost his job and 3 months earlier after the diagnosis of the rectal tumor. At this point, a diagnosis of conversion disorder manifested as a catatonic stupor was entertained. Lorazepam, 2 mg intramuscularly, was given, and 30 minutes later Mr. B was able to talk and reported feeling depressed because he viewed himself as a failure and as dependent on his sister. When questioned about his tumor, he denied having it but reported that his mother had died from a "stomach tumor." When questioned about his earlier muteness, he replied, "I just couldn't talk." The results of a mental status examination were essentially unremarkable. He did have symptoms of depression. The next day he relapsed after transfer to the psychiatry department, and he was treated with haloperidol and then with fluphenazine for 2 weeks because catatonic schizophrenia was suspected. However, at our request 2 mg of intramuscular lorazepam was administered, after which Mr. B was able to converse and was ambulatory. He was maintained on oral lorazepam. Five months later his catatonia was still in remission. His final diagnosis was adjustment disorder with depressed

Case 3. Mr. C, a 34-year-old man without prior psychiatric history, was admitted for evaluation of withdrawal, mutism, and inability to walk, which had lasted 3 months. His psychomotor retardation was marked, and his speech was slow. He described a power controlling him, making him unable to walk or talk, but denied having hallucinations. His affect was flat, and his cognitive function was intact. The results of physical and laboratory examinations were normal. An EEG revealed nonspecific slowing, and CAT scan results were normal. A diagnosis of catatonic schizophrenia was entertained. After admission, Mr. C became increasingly unresponsive, mute, and negativistic and refused to eat. Lorazepam, 2 mg intramuscularly, was administered, and 1 hour later Mr. C spoke and ate dinner. He received a total dose of 10 mg of intramuscular lorazepam over 48 hours, and he visited with his family and ate well. During the next 3 days, when lorazepam was withheld, he became unresponsive and withdrawn. He again received 2 mg of intramuscular lorazepam, and the results were similar. Lorazepam, 2 mg b.i.d., and haloperidol, 10 mg b.i.d., were then prescribed because of persistent delusions of control. Mr. C continued to improve without further relapse. His final diagnosis was schizophreniform disorder.

#### DISCUSSION

All three patients had signs of catatonic stupor without evidence for an organic etiology. The appearance of this behavior followed psychologically traumatic events in cases 1 and 2. Atri and Julius (6) reported a case of catatonic stupor secondary to use of maprotiline hydrochloride and thiothixene in which the EEG suggested seizure activity. However, in our case 1 the EEG was normal, and amitriptyline could not account for the catatonic behavior. All three of our patients responded to parenteral lorazepam in a similar fashion and within the same time range. In each case a relapse was noted when the effects of the drug wore off. Lorazepam seemed to disinhibit the inhibited behavior.

We believe that lorazepam, acting as a GABA facilitator, probably alleviated a dopamine blockage in the mesostriatal and mesolimbic systems, thereby stimulating the motor systems and releasing the inhibited catatonic behavior. There is evidence that GABA regulates dopamine activity in the mesolimbic and mesostriatal systems (2, 7) and that dopamine is essential for motor activity (5). Similarly, injections of a GABA agonist (muscimol) in the caudal ventral tegmental area of rats result in motor activity, aggression, and increased food intake, and this action is blocked by haloperidol (5, 7). We suggest that in catatonic states, parenteral lorazepam might be both diagnostically and therapeutically valuable. An average of three parenteral doses appear to be required for prolonged effects. It is more practical and safer than either intravenous diazepam or amobarbital sodium, which have been used in such cases (8, 9).

#### REFERENCES

- Greenblatt DJ, Shader RI: Prazepam and lorazepam: two new benzodiazepines. N Engl J Med 1978; 299:1342–1344
- Fricchione GL, Cassem NH, Hooberman D, et al: Intravenous lorazepam in neuroleptic-induced catatonia. J Clin Psychopharmacol 1983; 3:338–342
- Saklad SR, Ereshefsky L, Jann WW, et al: Usefulness of Injectable and Oral Lorazepam in Psychotic and Developmentally Disabled Patients. Austin, University of Texas Press, 1985, pp 1-21
- Morrison JR: Catatonia: retarded and excited types. Arch Gen Psychiatry 1973; 28:39–41
- Fricchione GL: Neuroleptic catatonia and its relationship to psychogenic catatonia. Biol Psychiatry 1985; 20:304–313
- Arri PB, Julius DA: Maprotiline hydrochloride associated with a clinical state of catatonia stupor and epileptic encephalogram. J Clin Psychopharmacol 1984; 4:207–209
- Garbutt JC, van Kammen DP: The interaction between GABA and dopamine: implications for schizophrenia. Schizophr Bull 1983; 9:336–353
- McEvoy JP, Lohr JB: Diazepam for catatonia. Am J Psychiatry 1984; 141:284–285
- Perry JC, Jacobs D: Overview: clinical applications of the Amytal interview in psychiatric emergency settings. Am J Psychiatry 1982; 139:552–559

# Absence of Acquired Tolerance to Neuroleptics in Schizophrenic Patients

Tom Palmstierna, M.D., and Börje Wistedt, M.D.

Development of increased tolerance to neuroleptics was investigated in 38 neuroleptic-respondent schizophrenic patients. At 5- or 8-year follow-up, clinical global assessments were related to changes in neuroleptic doses. In 93% of the patients gradually increasing tolerance could be excluded.

(Am J Psychiatry 1987; 144:1084–1085)

ong-term continuous treatment with neuroleptics → has been shown to be an effective way of minimizing the risk of psychotic decompensation in schizophrenic patients (1, 2). In spite of this benefit, longterm neuroleptic treatment has been criticized because of the side effects, mainly tardive dyskinesia (3). The question has also arisen as to whether increased tolerance to the effects of neuroleptics develops after longterm exposure. Analogous to the postulated nigrostriatal dopaminergic supersensitivity in tardive dyskinesia, the term "supersensitivity psychosis," or "tardive psychosis," was introduced by Chouinard et al. (4) in 1978 to describe a clinical syndrome possibly related to a similar condition in the mesolimbic pathways. Among the characteristics of this syndrome, it has been thought to be associated with the development of CNS tolerance to the antipsychotic effects of neuroleptics (5), which would have serious consequences for long-term treatment of schizophrenic patients, since numerous patients would then need gradually increasing doses to prevent deterioration.

This study was conducted to determine how common gradually increasing tolerance is over a long time in a well-defined schizophrenic sample.

#### **METHOD**

In 1978 the total schizophrenic population younger than 66 years in the catchment area of Västerås

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Central Hospital, Västerås, Sweden (approximately 150,000 inhabitants) consisted of 255 individuals. To perform a double-blind withdrawal study, all patients in this population were included who were outpatients stabilized on continuous neuroleptic treatment for more than a year, did not abuse drugs or alcohol, and had undergone treatment with depot neuroleptics (fluphenazine or flupenthixol) for at least the last 3 months. Of the 41 patients who met these criteria, 38 completed the withdrawal study, which has been presented previously (2). In this study, these 38 patients were followed up 5 (and in some cases also 8) years after entering the withdrawal study. It was possible to follow up 29 patients; seven of the missing patients were dead, and the remaining two patients were not traceable for other reasons. Diagnosis was in accordance with Bleuler's concept of schizophrenia, since research criteria, such as the Research Diagnostic Criteria (RDC), had not been introduced at the time of the withdrawal study. The patients' records were reevaluated later, and all the patients fulfilled the DSM-III criteria for schizophrenia.

For each of the 29 patients a standardized global impression assessment was performed at the beginning of the study and at follow-up. The patients were assessed with operationally defined criteria on three items: employment status, type of residence (i.e., independent living, sheltered living, mental hospital, short-term hospitalization for psychiatric intensive care), and overt schizophrenic symptoms. Each item is scored on a 4-point scale. For the purpose of this study, the patients were classified as either "deteriorated" or "unchanged/better" since the time of entering the withdrawal study. A "deteriorated" patient was defined as a patient who had deteriorated in at least one of the global assessment items given at the beginning of the study.

For comparison, all neuroleptic doses were converted into haloperidol equivalents according to the method of Suy et al. (6). An increased dose was defined as an increase of at least 50% since the beginning of the study, and a decrease was defined as a decrease to two-thirds or less of the original dose.

Serum levels of fluphenazine and flupenthixol were determined at steady state during treatment with depot medication before withdrawal in the original study.

All patients were followed up 5 years after entering

the original withdrawal study. Patients who then either were classified as deteriorated or had increased doses of neuroleptics were also followed up 8 years after entering the study to determine whether these changes were temporary or not. Patients who were unchanged or better with the same or lower dose were not followed up again, since they could not have been subject to increased tolerance to their neuroleptics.

#### RESULTS

At the 5-year follow-up, 20 patients (69%) had doses equally or less potent than those at the beginning of the study and had unchanged or better clinical conditions. The remaining nine patients were also followed up 8 years after entering the study. At the 5-year follow-up, four of these nine were unchanged or better and had increased doses. At the 8-year follow-up, they were all still unchanged or better and had no further increases in dose. These four patients all had serum neuroleptic levels in the lower part of the range of serum levels. For three of these patients, who were receiving fluphenazine at the beginning, a statistical test, the Mann-Whitney U test, could be performed. (The fourth patient in this category was the only patient from the original flupenthixol group; therefore, it was not possible to perform a statistical test.) In the test, these three patients had significantly lower serum fluphenazine levels than the other 14 originally receiving fluphenazine (U=4, p<.05, one-tailed test). The mean±SD levels of the respective groups were  $0.67\pm0.13$  and  $1.30\pm0.49$  ng/ml.

At the 5-year follow-up, two of the patients were deteriorated and had decreased doses. At the 8-year follow-up, these patients had returned to their original clinical conditions and were still receiving doses lower than those at the beginning of the study. The remaining three patients had all deteriorated by the 5-year follow-up in spite of increased doses of neuroleptics. At the 8-year follow-up, one of these three patients had managed to return to her original clinical condition without any further increase in dose. The other two patients in this category were the only two patients in

the whole follow-up sample who needed gradually increasing doses, and they were both still deteriorated at the 8-year follow-up.

#### **DISCUSSION**

Our results from this long-term follow-up study of neuroleptic-respondent schizophrenic patients indicate that acquired neuroleptic tolerance is not common. Only two patients needed gradually increasing doses of neuroleptics; i.e., 27 (93.1%) of our 29 follow-up patients did not need gradually increasing doses to remain in a stable clinical condition or to prevent deterioration. Also, the need for increasing doses to remain stable throughout the study was probably due to pharmacokinetic factors, since these two patients had lower serum levels of neuroleptics than the other patients followed up. Of course, these findings cannot exclude the existence of tardive psychosis, but since one of its essential features is acquired tolerance to the effects of neuroleptics, our results contradict the assumption that this syndrome could be fairly common (5). On the contrary, our results tend to indicate that most patients can safely receive the same doses for long periods without a weakening in the effect of their medication.

#### REFERENCES

- 1. Davis JM: Overview: maintenance therapy in psychiatry, I: schizophrenia. Am J Psychiatry 1975; 132:1237–1245
- 2. Wistedt B: A depot neuroleptic withdrawal study: a controlled study of the clinical effects of the withdrawal of depot fluphenazine decanoate and depot flupenthixol decanoate in chronic schizophrenic patients. Acta Psychiatr Scand 1981; 64:65-84
- 3. Gardos G, Cole JO: Maintenance antipsychotic therapy: is the cure worse than the disease? Am J Psychiatry 1976; 133:32–36
- Chouinard G, Jones BD, Annable L: Neuroleptic-induced supersensitivity psychosis. Am J Psychiatry 1978; 135:1409– 1410
- Chouinard G, Jones BD: Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 1980; 137:16–21
- Suy E, Woestenborghs R, Heykants J: Bioavailability and clinical effect of two different concentrations of haloperidol decanoate. Curr Ther Res 1982; 31:981–991

# New Female Perceptions of Parental Power

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In a study of family roles, 85 adolescent sons and daughters from 27 families initially attributed "power" roles to fathers and "support" roles to mothers. Three years later, daughters perceived power and support roles as shared, while sons still perceived the earlier dichotomy.

(Am J Psychiatry 1987; 144:1086-1087)

Until recently, normal adolescent development was generalized from clinical work with patients (1). Similarly, the psychology of women was traditionally judged against the standard of male personality. Studies of men were generalized to women, who sometimes appeared as developmentally deficient men. Recently, Gilligan (2) has legitimized male-female differences as normal variations—e.g., whereas males traditionally interpret themselves in terms of "separateness," females traditionally operate through a sense of "connectedness" with others. However, even today current knowledge of maturation into young adulthood is based primarily on studies of middle-class Caucasian males; few, if any, studies have considered non-Caucasian ethnic groups or compared males with females.

This report is part of the ongoing Hawaii Family Research Project, which attempts to provide a firmer basis for understanding male and female personality development as well as family functioning. Previous reports have demonstrated normal variations of family attitudes and behaviors in different ethnic groups (3) and variations in defining goals related to autonomy and differentiation (4) and have also shown that young adolescent men and women differ in the rate, degree, and manner in which they achieve separation from the

nuclear family (5). While the latter findings have paralleled those of Gilligan, in this report we present data from a 3-year follow-up study that focus on the appearance of a new male-female difference during maturation.

#### **METHOD**

The Hawaii Family Research Project originally surveyed 407 families with a questionnaire aimed at identifying differences between ethnic groups (4) and the sexes (5). Twelve families from each of four ethnic groups were then selected for more intensive study (3). In the families selected, both parents belonged to the same ethnic group and were living together, there were at least two unmarried adolescent children in the home, and neither children nor parents had any obvious psychiatric disorder or record with the law. Of these 48 families, 27 were available for follow-up after 3 years (54 parents and 85 offspring, 47 sons and 38 daughters).

Scores on the California Personality Inventory placed the entire sample within the broad category of normal, functional, and healthy. Socioeconomic ratings placed the families in a broad middle-class category.

The focus of this report is on the 3-year follow-up of selected data from the sociogram, which were subjected to chi-square analysis. Each family member independently completed a 20-question sociogram questionnaire designed for the research project to examine intrafamily relationships. Each subject was asked to identify a family member—"mother, father, brother, sister, self, or no one"-for 20 specific family roles (see table 1 for sample questions). For the purpose of analysis, the questions were grouped into the categories of power, support, intimacy, and independence. Those relating to power and support will be the focus of this report. Each family member completed the sociogram twice, first during the initial phase of the intensive study of 48 families and again 3 years later in the follow-up of the 27 available families.

The limitations of both the sociogram and the subject sample are recognized. The sociogram questionnaire is a forced-choice subjective assignment of family roles, not an objective record based on family

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TABLE 1. Parent Identified by Sons and Daughters as Filling Family Power and Support Roles in Initial and Follow-Up Surveys of 27 Families

	Initial Si	ırvey	Follow-Up Survey		
Offspring's View of Parental Role	Parent Most Often Identified	$\chi^2$ $(df=2)^a$	Parent Most Often Identified	$x^2$ $(df=2)^a$	
Sons (N=47, average age at follow-up=23.3 years)					
Power roles					
Who is the most responsible?	Father	8.72 <sup>b</sup>	Father	7.91°	
Who exercises the strongest influence in family decision making?	Father	7.20 <sup>b</sup>	Father	14.25 <sup>b</sup>	
Who could best solve a money problem? <sup>d</sup>			Father	17.36 <sup>b</sup>	
Support roles					
To whom would you go to discuss a serious problem?	Mother	5.57	Mother	9.48 <sup>b</sup>	
Who always has the best interests of the family in mind?	Mother	9.77 <sup>b</sup>	Mother	8.27	
Who is most apt to notice when you have a personal problem?	Mother	15.75 <sup>b</sup>	Mother	16.75 <sup>b</sup>	
Daughters (N=38, average age at follow-up=23.2 years)					
Power roles					
Who is the most responsible?	Father	8.78 <sup>b</sup>	Equal	5.12	
Who exercises the strongest influence in family decision making?	Father	23.44 <sup>b</sup>	Equal	9.68	
Who could best solve a money problem? <sup>d</sup>			Mother	5.56	
Support roles					
To whom would you go to discuss a serious problem?	Mother	38.11 <sup>b</sup>	Mother	8.82 <sup>b</sup>	
Who always has the best interests of the family in mind?	Mother	23.23 <sup>b</sup>	Mother	3.70	
Who is most apt to notice when you have a personal problem?	Mother	35.41 <sup>b</sup>	Mother	13.73 <sup>b</sup>	

<sup>&</sup>lt;sup>a</sup>One-sample comparison of observed and expected responses.

behavior. Furthermore, the sample size is limited and confined to middle-class families.

#### **FINDINGS**

Significant differences between sons and daughters were found to emerge over the 3-year study period (see table 1). Initially, both sons and daughters differentiated between their parents for major family functions, choosing mothers for support roles and fathers for power roles. After 3 years (from late adolescence to young adulthood), both sons and daughters continued to view their mothers as the major support figures. However, while the sons continued to differentiate between their mothers and fathers in assigning major roles of support and power, the daughters did *not* distinguish between their mothers and fathers for power roles, choosing one as often as the other.

#### DISCUSSION

What can we make of this finding? It extends Gilligan's work in suggesting that young males continue to remain role oriented as they mature, while young women begin to shift from this orientation. It suggests a persistent perception in our young men of a sharp male-female boundary for the major family role of power, while our young women became less able or less willing to make such sharp role distinctions.

The specific shift to a less differentiated perception of power distribution by the young women in our study supports the contemporary notion of social change toward functions no longer clearly split by sex. Our female subjects may reflect a need for change, rejecting the traditional assignment of power to males, while the males hold on to role perceptions that have traditionally given them power and status.

This finding may suggest a difference in the way young men and women are separating from their families of origin. This process may be changing more rapidly in females than in males—as reflected in their greater perception of change in the traditional distribution of power in the family—and has implications for their own future family roles.

These data support the notion of a shift toward merging family roles in young women but not young men. This may herald an era of greater compatibility and equality of the sexes, but it may also foretell an era of friction between the sexes until a new balance is established. Further research may provide more specific answers to these questions.

#### REFERENCES

- 1. Offer D, Ostrov E, Howard KI: The Adolescent: A Psychological Self-Portrait. New York, Basic Books, 1981
- Gilligan C: In a Different Voice. Cambridge, Harvard University Press, 1982
- Hsu J, Tseng W-S, Ashton G, et al: Family interaction patterns among Japanese-American and Causasian families in Hawaii. Am J Psychiatry 1985; 142:577-581
- 4. McDermott JF, Char WF, Robillard AB, et al: Cultural variations in family attitudes and their implications for therapy. J Am Acad Child Psychiatry 1983; 22:454–458
- McDermott JF, Robillard AB, Char WF, et al: Reexamining the concept of adolescence: differences between adolescent boys and girls in the context of their families. Am J Psychiatry 1983; 140:1318-132

<sup>&</sup>lt;sup>b</sup>p≤.01.

<sup>°</sup>p≤.02.

<sup>&</sup>lt;sup>d</sup>Question included only in follow-up survey.

### Book Forum

### Nancy C. Andreasen, M.D., Ph.D., Editor

#### **PSYCHOTHERAPY**

Making Contact: Uses of Language in Psychotherapy, by Leston Havens. Cambridge, Harvard University Press, 1986, 195 pp., \$18.50.

This highly original book, filled with illuminating clinical examples, is actually a primer of grammar and rhetoric for the psychotherapist. Leston Havens has gone well beyond our usual descriptions of therapeutic interventions as interpretations, confrontations, clarifications, etc. He has devised a systematic classification of the language of therapy based on the core aims of reaching and freeing the patient to develop an esteemed self capable of a broader range of hopes, feelings, and actions. Uniquely, as far as I know, he has developed a theory of therapeutic rhetoric to help therapists choose their words, phrase their sentences, and modulate their tone of voice and manner of speech to achieve specific therapeutic goals. Havens's therapy is entirely rooted in psychoanalytic theory and particularly influenced by the existential and interpersonal schools, but he acknowledges his debt to Freudian ego psychology, object relations theory, Winnicott, Kohut, and others. In Havens's hands, this breadth of theoretical views is not a simple eclecticism but the carefully considered base for his theory and description of the mode of action of therapeutic interventions. We are also given glimpses of the work of an artist-therapist who has crafted a personal style of great power and who consistently provides the data on which his new ideas are based.

The core of this volume is Havens's description of three forms of therapeutic language—empathic, interpersonal, and performative. About each of these Havens has important insights and gives helpful descriptions of how to say things to different patients at various stages of treatment. For example, in the section entitled Empathic Language, he says, "Cognitive empathy, where the therapist silently completes the patient's sentences, is both the most precise and the least used method of testing. It is a form of mind reading" (p. 27). He describes a number of types of empathic statements, one of which is the "imitative statement." Here the therapist speaks in the first person for the patient in the persona of the patient. For instance, the therapist might say, "Can I love him?" and "Aren't I beautiful?" to a young woman, voicing her thoughts, or, "Why can't I be loved?" and "What can one expect of this bloody world?" and "I have no rights" to a young man, voicing his unspoken thoughts. To me, such interventions at first seemed startling, and I felt that they were somewhat manipulative, perhaps infantilizing. I could imagine Dr. Havens saying these things, but I could not imagine myself doing so. By the end of the book, however, as I appreciated the powerful consistency of Havens's determined effort to make contact with the patient at the point where the patient exists emotionally and interpersonally, these phrases began to seem appropriate and perhaps possible even for me.

Another form of empathic statement that Havens describes is "translations": "A translation is the rendering of

the patient's state of mind into words. The most succinct of these translations are ... exclamations ... such as 'How wonderful!' or 'Terrible!' said with appropriate feeling" (p. 44). Havens is interested in using language in ways that match the affective experience of his patients, and he doesn't hesitate to instruct that "declarative sentences, such as 'That's awful,' must be said expressively in order to do their empathic work" (p. 45). There is nothing laid-back about Havens's therapeutic recommendations, and he is not romantic about the doctor-patient relationship: "It is not enough to say that psychotherapy depends on respect, even appreciation . . . . A central contention of this book is that power can only be opposed powerfully, meaning that the therapist must have power and use it. Empathy may be necessary to find the patient, but then the patient may need to be defended against overpowering forces—or patient and therapist may need to be defended against one another" (p. 88). It is refreshing to find this stated so clearly.

Each section of this book is packed with descriptions and examples, and I can give only a hint of its clinical richness. There are clear descriptions of interpersonal language (those statements intended to modify the relationship to another person, especially the therapist) and performative language (statements intended to change something outside oneself), including their psychodynamic rationale, instructions for their use, and illustrations with exquisite clinical vignettes. Havens offers fascinating discussions on the treatment of very sick paranoid and schizoid patients and on the handling of the transference psychosis. From his own experience, he is passionately convinced of the power of psychotherapy, and he believes that too many therapists are using medication and electricity in lieu of sharpening the psychotherapeutic skills that might enable them to treat their patients.

This volume is clearly the result of a lifetime of experience. It systematizes and categorizes what a wise (and, perhaps in spite of himself, a charismatic) therapist does to help his patient. Some inconsistencies in theoretical viewpoint between the beginning and end of the book undoubtedly reflect the gestation time of this work and in no way damage the presentation of the major themes. The writing is admirably lucid and simple, and those of us with less experience—or less sheer therapeutic talent—may be beguiled into thinking we can quickly achieve the therapeutic dexterity of the master therapist that Havens is. The intricacy of an art is not always apparent on its surface. Havens is recommending powerful medicines, and the inexperienced therapist is welladvised to proceed with caution before trying to imitate him. Even the most experienced therapist, however, will learn new things, will rethink the ways he or she talks to patients, and will do better work after studying this book. Besides its obvious clinical value, this monograph opens the way to new and better study of the effective elements of therapeutic action. This is a most important contribution and I highly recommend it.

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Practical Psychotherapy, by Myron F. Weiner, M.D. New York, Brunner/Mazel, 1986, 314 pp., \$30.00.

What does one do if one does not know what to do? Let's say, in treating patients who cannot afford, do not want, or are unsuitable for psychoanalysis or, for that matter, psychoanalytically oriented long-term or even short-term psychotherapies—patients with physical illnesses, psychosis, or severe borderline disorder? What Dr. Weiner describes in detail in this book as repressive and ego-supportive psychotherapies are practical guidelines for dealing with such patients.

The author begins by providing some basic information on psychopathology, sprinkled with a number of schemata that portray psychological developments and adaptations, conflicts, and models for health and illness as a useful prelude to the establishment of a frame of reference for his practical approach to psychotherapy. However, the appendix providing four psychometric tests at the end of the book is rather a non sequitur. The substance of the book is in between these two and filled with clinical examples and wisdom.

Dr. Weiner's book on practical psychotherapy comes with high praise from two noted clinician-teacher-scholars—Irvin D. Yalom and Benjamin J. Sadock—and rightly so. In the finest tradition of Adolf Meyer and Jules Masserman, Dr. Weiner's book is embedded in psychobiological and biodynamic approaches and provides guidelines for the treatment of patients who are less likely to benefit (if not be harmed) by typical psychoanalytical techniques. Although he believes that thoughts, feelings, and behavior are influenced (not determined) by unconscious motivation and conflict, Dr. Weiner does not support the resolving of conflicts through regression, transferential neuroses, or insight. In fact, he could have named the book Against Regression or Against Insight.

Dr. Weiner blends the work of humanists such as Carl Rogers and Heinz Kohut and existentialist therapists such as Irvin Yalom to propose that the therapist should experience the patient as a real person (and vice versa), help to integrate the patient's sense of self, and teach coping skills through interactional feedback. After all, psychotherapy is a form of education.

The literature on psychoanalysis and psychotherapy is heavily inundated with writing on the theory of mind. Occasionally, one comes across a book written by a real clinician who sees real patients and offers unapologetically unorthodox but practical suggestions to the really bewildered therapist. This is such a book. Here, "practical" means incorporating intrapsychic, interpersonal, and milieu therapies and pharmacological interventions and, at times, siding with the neurotic needs of the patient, manipulating the patient's environment, directly teaching, and encouraging repression. Myron Weiner's therapist is not equidistant from the ego, the superego, and the id as a neutral observer, clarifier, and interpreter. In fact, his therapist may join with one or the other, temporarily or permanently, depending on the patient's strengths and pathology. He or she may encourage obsessive patients to feel, may encourage histrionic patients to think, may accept a paranoid patient's view of the world, and may challenge the depressive patient's view.

How does one do all this and still manage the transferential entanglements? Dr. Weiner considers the interactive style of ego-supportive psychotherapy a form of optimal transference gratification, which may help limit both eroticized transference and negative transference. The therapist, by being helpful, stimulates these positive feelings

toward himself or herself. Meanwhile, enough of a barrier is maintained to prevent the therapy from becoming a social relationship. Tough task. Could only the ideal therapist, described in detail in the book, accomplish this? Is there not a negative transferential disposition that even an ideal therapist could not avoid without premature termination or compromise of the therapy?

Its clinical reality and practicality are no doubt the strengths of this book. In an effort to be "ego-supportive" to his readers, Dr. Weiner also provides a theoretical scheme to condense and simplify matters for easier learning; this, however, appears to go beyond the state of the art and is somewhat confusing. He makes a distinction between egosupportive and ego-repressive types of psychotherapy, using the latter term where others would simply use the term "supportive." There is even a technical point that I believe actually contradicts Kernberg's own description of his work with patients with borderline disorder. On page 182 Dr. Weiner states that Kernberg's studies conclude that an ego-supportive therapy offers more hope than a repressive therapy for patients with severe personality disorders. It is my understanding that Kernberg stated, rather, that supportive therapy is contraindicated in favor of a "purely expressive approach" (1).

In all, however, Dr. Weiner's book is very helpful.

#### REFERENCE

1. Kernberg O: The theory of psychoanalytic psychotherapy, in Curative Factors in Dynamic Psychotherapy. Edited by Slipp S. New York, McGraw-Hill, 1982, p 32

TOKSOZ BYRAM KARASU, M.D. Bronx, N.Y.

Therapeutic Factors in Group Psychotherapy, by Sidney Bloch and Eric Crouch. New York, Oxford University Press, 1985, 325 pp., \$27.95.

This scholarly book presents a critical evaluation of clinical lore, theory, and empirical data concerning the process elements of group psychotherapy that exert beneficial influence on group members. Beginning with a thorough presentation of the history of group psychotherapy, Bloch and Crouch trace the development of contemporary conceptualizations of the therapeutic factors in group psychotherapy. They critically examine nearly 100 clinical and analogue research investigations, giving special emphasis to methodological quality, soundness of conclusions, and applicability to clinical practice. A notable feature is the summarization of these studies in an appendix that highlights the subjects, methods, and findings in an extended table, thus avoiding unnecessary saturation of the text while facilitating overview and comparison.

To the authors' immense credit, they focus on the common mechanisms of therapeutic change rather than dwelling on theoretical, stylistic, or technical disagreements. Ten therapeutic factors (insight, learning from interpersonal interaction, acceptance, self-disclosure, catharsis, guidance, universality, altruism, vicarious learning, and instillation of hope) are each carefully defined and critically evaluated in terms of relevant theory and data. This fine-grained analysis differentiates and extends previous constructs, showing factors to consist in an enormously complex set of subfactors. However, the sum total of empirical knowledge distilled from this

analysis is quite modest. Bloch and Crouch essentially conclude that "some form of insight appears to be linked to improvement; acceptance and self-disclosure are also relevant, though to a lesser degree. . . . Guidance and vicarious learning emerge repeatedly as unhelpful components in all types of group treatment" (p. 247). Unsatisfying though such conclusions are, we are nonetheless disabused of unproven notions about the presumed agents of therapeutic change.

Bloch and Crouch offer important suggestions for future research, such as clear operationalization of concepts, crossvalidation of studies, and an intensive focus on the measurement of process phenomena. However, the major limitation of this line of research may not be of a technological nature but, rather, may be a consequence of the basic conceptualization of therapeutic factors as "a finite number of elements distinguishable from one another by virtue of their highly specific effects on the group member" (p. 2). Although this view fits our contemporary research Zeitgeist, the nature of behavioral mechanisms may ultimately preclude specification of such a set of discrete factors. It seems unlikely that any researcher will be able to make statements about specific therapeutic factors which are not endlessly contingent on further statements about the other conditions and characteristics which make up the total system of the group and within which the group functions. Bloch and Crouch wisely acknowledge the ultimate unsuitability of examining any factor in isolation, yet their analysis of the published literature on interaction of discrete factors yields little additional knowledge. Nonetheless, these authors believe that this accepted paradigm, with certain procedural improvements, can eventually tease apart the therapeutic mechanisms into discrete elements.

These reservations notwithstanding, this thoughtful volume presents a thorough compendium of the relevant research. Although clearly not intended as a "how-to" book, it does contain substantial material of use to clinicians as well as to educators and researchers. Bloch and Crouch are obviously independent thinkers who do not shrink from drawing warranted conclusions or from offering reasonable conjectures regarding ambiguous or contradictory research data. Their methodical, incisive approach will sharpen our concepts and encourage us to critically rethink our notions about the therapeutic factors in group psychotherapy.

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Psychology of the Self and the Treatment of Narcissism, by Richard D. Chessick, M.D., Ph.D. New York, Jason Aronson, 1985, 358 pp., \$35.00.

Except for the demands of reality, I was unable to put this book aside. The author is a scholar, a teacher, a clinician, and a writer of substance. His goal here is a comprehensive introduction to Heinz Kohut's "psychology of the self" and the clinical treatment of narcissism, and he succeeds handsomely. The book is well organized and readable. Its four sections cover different aspects of narcissism, Kohut's work, clinical applications, and clinical evaluations.

Chessick places Kohut's views in historical perspective by comparing and contrasting them with those of Freud, Melanie Klein, Kernberg, Lacan, Fairbairn, Balint, and many other theorists and practitioners. Chessick presents Kohut's theories clearly and objectively. The case of Mr. Z, which solidified Kohut's orientation, consisted of two analyses; the

second is considered "successful" with a follow-up of 10 years and illustrates his technique. As Chessick explains, mothering is emphasized for the formation of "self." Animal desire, not libido, is the human "force." The supraordinate bipolar self, which is the central mental structure, is composed of the grandiose self (ambition) and the internalized idealized parent (guide and ideals). Especially controversial is the caring concept of empathy, "the indispensable tool of observation." By transmuting internalization of the transference through understanding, explanation, and its natural healing power and without active soothing, it corrects threats to the nuclear self. Kohut rejected the Oedipus complex as the nucleus of character disorders and narcissism and was critical of the authoritative, aloof traditional analysts and their middle-class values. Cure, he insisted, is not as dependent on cognition and interpretation as it is on empathy. Cure results in the capacity for achievement, pleasure, and making the right choices.

Chessick describes the criticism of Kohut's work by analyst theorists as "bitter." Critics claim that Mr. Z's two analyses were really one, and, if "successful," the second analysis was more properly performed. Critics also charge that Kohut's new words are simply changes of Freudian terminology and that his ideas are unclear, ambiguous, and mystical. Empathy is nonanalytic, noninterpretative, and noninsightful, contaminating the transference and resulting in a collusion between patient and analyst to hide oedipal hostility. Therefore, it is not psychoanalysis. Chessick states that this conclusion is as much political as it is theoretical.

The struggle is not new. Patients, like the character in *Macbeth*, seek a "sweet oblivious antidote," and the physicianly drive is to provide it. Freud (1) warned about transference cures and recommended the "gold of analysis and the copper of suggestion" for wider clinical analytic application. Alexander argued that his corrective emotional experience was not a "flight into health" (2). Chessick declares he is not a disciple of Kohut, but he concludes that "self-psychology seems to work consistently." To my knowledge, no systematic study of any psychotherapy has included control subjects, dropouts, treatment failures, and a statistically significant number of patients to provide scientific validity of any cure. Nevertheless, cures are claimed. The 10-year follow-up of Mr. Z, which fulfilled Kohut's definition of cure, does not prove the validity of his method. Nor does claiming something to be psychoanalysis make it psychoanalysis.

To the "purists," Chessick claims, Kohut holds a smoking gun. The reaction is "fierce" and "bitter" criticism, whereas in other scientific ventures, the debate is called "spirited." It is probable that empathy may make psychoanalysis more applicable and palatable for those patients who are unsuited for "purist" analysis. Patients with the same diagnoses still vary, and analysts with similar training also vary. Kohut, a most charismatic, devoted, and caring therapist, recognized the need for empathy. His use of psychodynamics with empathy could be psychoanalysis with a parameter, but he eschewed fundamentals of psychoanalysis and so, according to the strict interpretation of the "purists," his concepts led to transference cure. Having been reared in psychoanalysis and convinced that it provides the best understanding of psychopathology, I agree. Empathic attention is timely, however. It is a welcome permission for warmth to patients, to trainees, and to practitioners without active "soothing."

Chessick's book is a gem. All psychotherapy students and practitioners of all persuasions will find it helpfully informative and stimulating.

#### REFERENCES

 Freud S: Lines of advance in psycho-analytic therapy (1919), in Complete Psychological Works, standard ed, vol 17. London, Hogarth Press, 1955

Train GJ: Flight into health, in Encyclopedia of Psychoanalysis. Edited by Eidelberg L. New York, Free Press, 1968

> GEORGE J. TRAIN, M.D. New York, N.Y.

A DSM-III Casebook of Differential Therapeutics: A Clinical Guide to Treatment Selection, by Samuel Perry, M.D., Allen Frances, M.D., and John Clarkin, Ph.D. New York, Brunner/Mazel, 1985, 370 pp., \$37.50.

This book is a follow-up volume, developing on ground initially laid in *Differential Therapeutics in Psychiatry* (1). The authors' current effort is excellent, and I highly recommend this book to all practitioners interested in general psychiatry. It is filled with sound clinical precepts, consistent practical wisdom, and an overall tone of logic and compassion. The similarity of the text's organization to the psychiatric specialty Board examinations may give it a particularly strong appeal for those psychiatrists preparing for this examination (especially part II).

The text is organized into sections and chapters that parallel the organizational scheme of DSM-III itself (for example, there are sections entitled Organic Mental Disorders, Substance Use Disorders, Schizophrenic Disorders, etc.). Specific chapters within a section are devoted to various DSM-III diagnoses, and all discussions are anchored to specific, invariably well-selected clinical cases. In each chapter, the authors propose a DSM-III diagnosis (along each axis) and discuss a differential treatment plan that flows logically from the facts of the case. In these discussions, I believe, one finds the book's greatest contribution and strength. The treatment plans in these chapters address therapeutic strategy in DSM-III language, but the plans themselves are never stereotyped or "cookbook." This lack of reductionism is critical, in my view, at this stage in psychiatry's history and may be especially critical in a text purporting to apply treatment strategies derived from a purely phenomenologic source (DSM-III).

The book has 16 chapters covering what the authors regard as important DSM-III diagnoses. No attempt is made to be encyclopedic. Rather, emphasis is based on clinical relevance, so that some diagnoses (e.g., alcoholism) get more than one chapter, and other diagnoses are not specifically addressed (e.g., multiple personality). Some readers may regard the book as flawed in this regard (it is not comprehensive), but I regard the pruning that the authors have undertaken as valuable. In my view, this renders the book more pertinent and readable. Those seeking an encyclopedic text can, and should, look elsewhere.

The chapters have titles that may remind some of a series of novels by Erle Stanley Gardner: "The Case of the Disruptive Daddy" and "The Case of the Love Junkie," for example. This attempt to capture the reader's interest may strike some as too "cute," but I believe serious readers should not be deterred. The case format is, I think, an attempt to anchor theoretical discussion firmly in the complex and genuinely fascinating realm of real people in believable human contexts, just as psychiatrists encounter them. Although the chapter titles may seem too catchy, the case vignettes themselves are well developed and show

unmistakable verisimilitude. The cases are clear and well written. Their presence at the outset of each chapter definitely draws the reader in. The chapters then have much to teach.

The book has been well edited for style and is unusually clear and well written compared with most texts. It manages to be lively while still covering the facts. To an extent unusual in multiauthored texts, there is stylistic consistency.

The greatest value of the book for me personally lay in the considerable wisdom and clinical common sense of the authors. The book strikes me in some ways as similar to a series of high-quality clinical grand rounds. The authors address a range of diagnoses and clinical material with intelligence, up-to-date knowledge, and perspective. In this regard, I found the first chapter of the book to be so newhat anomalous, addressing theory and pedagogical pulosophy with far less clinical immediacy than the remaining chapters. Perhaps there are those who will find this first chapter clarifying, but I fear it may be off-putting to readers like me who learn best "at the bedside." Many readers tend to cathect a book, if they are going to, in the first chapter. It would be unfortunate if some individuals ended up putting the book away prematurely because of the apparent density of its opening pages.

A more undebatable drawback to the book is its lack of indexing. I found the book valuable enough that I later sought its counsel regarding a specific clinical situation. Looking for an index, I found there was none. This book is good and deserves better referencing.

In summary, this volume builds on the previous volume written by the authors. It does so by applying sophisticated clinical reasoning, based on *DSM-III* conceptualizations, to actual clinical material. The text succeeds in doing this in a lively, vivid, stylistically satisfying manner that will bo'd the interest of potential Board examinee and advanced psychiatric clinician alike. It is an excellent book that will be improved in later editions by the addition of a good index.

#### REFERENCE

 Frances A, Clarkin J, Perry S: Differential Therapeutics in Psychiatry: The Art and Science of Treatment Selection. New York, Brunner/Mazel, 1984

DAVID E. REISUR, M.D. Deni er, Colo.

Piagetian Dimensions of Clinical Relevance, by Hugh Rosen. New York, Columbia University Press, 1985, 258 pp., \$30.00.

The concept of basing a general theory of psychopathology on the work of the Swiss cognitive psychologist Jean Piaget seems to me an unlikely venture for several reasons. Not the least of these stems from my one persona exposure to Piaget when I heard his plenary address to the American Psychoanalytic Association in 1970. To that forum Piaget confessed that his interest in psychopathology had been greatly limited by his response to his mother's severe mental illness, which he felt had made him phobic about psychiatric conditions. Furthermore, his work, although developmental, always concentrated on the sequence in which children's cognition can be seen to develop without reference to their emotional stability or the stability of the parental environment. Piaget's work, although "objective" in studying the

process of how our thinking capacities develop, is nonetheless the result of his study of his own children. He presented them with a series of tasks that in turn would demonstrate limitations in their capacity to think abstractly at various ages. Individuals with the view that cognition rather than affect is central to the human condition are more likely to entertain the idea that the results of such observations could possibly generate a meaningful system or theory of psychopathology. Therefore, there is is an unavoidable conflict with theorists who concentrate on the early developmental matrix in terms of drives or object relations evolving around the dual affective axes of love and aggression and resulting in the formation of either a healthy or a pathological self.

Hugh Rosen, the author of this promisingly titled book, although stressing Piaget's view that affect and cognition cannot develop separately, ascribes a central position to cognition in the etiology of psychopathology and in its psychotherapeutic amelioration. It is unclear, however, that this position represents what Piaget himself would have put forward with regard to psychopathology and psychotherapy. Rather, it appears to be the result of Rosen's application of Piaget's work to these, for Piaget, "foreign territories." The reader will find an excellent summary of Piaget's observations and theories about the stages of cognitive development. Furthermore, Rosen supplements Piaget's findings with those of other workers in the area of cognition who have expanded Piaget's contribution or contributed original ideas of their own. The book contains useful summaries of Kohlberg, Gilligan, Kegan, and Greenspan, to name a few.

The most significant chapter in the book for most readers of this journal is "Piagetian Perspectives on Psychotherapy and Other Interventions." Here Rosen intends to satisfy the promise of the title and give those of us whose central orientation is that of clinical practice a chance to evaluate the way in which the previous five chapters of information can be used. Despite the presence of a subsection entitled Integrating Piaget and Psychoanalysis, Rosen ignores the fundamental contradictions between depth-oriented, dynamic psychoanalytic approaches and those of so-called cognitively oriented schools. Although the psychoanalysts he quotes, such as Greenspan and Anthony, have been drawn to the concept of developmental stages, they have not retreated from the centrality of emotions, particularly those related to early figures in the child's emotional life and development. Rosen views Beck's "cognitive therapy" as the ultimate

Rosen views Beck's "cognitive therapy" as the ultimate expression in psychotherapeutic technique of Piagetian theory. Beck's cognitive therapy, with its emphasis on unhealthy patterns of thinking as sufficient to satisfy etiological questions, is a form of therapy that can be effective with a large range of patients who are amenable to a relatively short-term attempt to influence their emotional suffering. Although it has an appeal as a relatively simple approach to psychoneurotic problems, it can in no way offer itself as a major competitor to more depth-oriented dynamic orientations.

In my opinion, Rosen is too eager to connect Piaget with current cognitive therapies. Although these therapies undoubtedly have some clinical effectiveness and relevance, the implication that they can stand on their own as systems or theories of psychotherapy ignores 85 years of theoretical development within psychoanalysis. It is unclear that Piaget would approve of such an omission. It is probable that in another interpretation of Piaget's relevance to dynamic psychotherapy, an adaptation of stages of emotional growth could be arranged in a system parallel to that devised by Piaget for cognition. Whether and to what extent this would

differ from Anna Freud's developmental profile would be interesting to speculate on.

This book illustrates the problem of competition between forms of psychotherapy. Competition, by its very nature, may be inevitable and useful in the development of psychotherapeutic techniques. However, when, as in this book, an author pays inadequate attention to important and fundamental developments that preceded the "new" contribution, the result is to devalue established clinical therapeutic principles of theory and technique. Rosen states that "the Piagetian paradigm does not require of the clinician that he abandon what he already believes and practices in favor of the cognitive, structural, developmental perspective." However, he adds that the paradigm does "beckon him to coordinate this perspective with his current orientation in order to reequilibrate towards a higher level of equilibrium." This statement seems to invite clinicians to add Piaget and cognitive therapy to their technical and theoretical knowledge as if their current theoretical orientation were unsatisfactory and deficient. Such an assertion denies the degree to which the ability to think well, accurately, and abstractly has, historically, always been viewed as the product of a successful psychoanalytic psychotherapy. The proof that Piaget's theories of cognition contribute meaningfully to our clinical work fails in this book because of Rosen's lack of attention to the depth of contributions within the area of dynamic psychotherapy that precede and should inform his interpretation of the role of cognition in psychotherapy. Unfortunately, although this book provides a good summary of the work of Piaget and his followers in the area of cognitive research, readers searching for convincing "clinical relevance" will be disappointed.

HENRY J. FRIEDMAN, M.D. Cambridge, Mass.

#### NEUROPHARMACOLOGY

Drugs in Central Nervous System Disorders, edited by David C. Horwell. New York, Marcel Dekker, 1985, 332 pp., \$65.00.

Books on clinical neuro- and psychopharmacology are not uncommon, but good ones are. So we naturally wonder whether this new contender might supplement or even replace the standard texts by Baldessarini (1) and Hollister (2) on the clinician's bookshelf. After all, the editor's preface promises that the book will "review and update the information available from the literature on the major drugs used in the treatment of disorders of the central nervous system" and that the focus will be on the drugs' "efficacy, major side effects, dosage, mode of action, preferred routes of administration, and the special features that affect their pharmacodynamic, pharmacokinetic, and metabolic fates." Now, there's a book we could really use if it delivered the goods.

But it doesn't. Uneasiness first sets in when we notice that the editor is a medicinal chemist rather than a clinical pharmacologist or an academic physician. Then there's the peculiar choice of drugs covered and the wildly vacillating depth of coverage. Antidepressants and centrally acting analgesics are around as expected, but anxiolytics and anticonvulsants are represented solely by the benzodiazepines and the barbiturates. Neuroleptics have a chapter of more than 100 pages, but lithium receives two pages, L-dopa

gets one, and clonidine, methylphenidate, L-tryptophan, and ergoloid mesylates have two lines each. Phenytoin, carbamazepine, valproate, blockers, cyproheptadine, and antimigraine drugs—not exactly obscure or obsolete CNS medications—are absent altogether. A puzzling chapter on "Drugs Used in the Regulation of Endocrine and Motor Activity" (a novel pharmacological category) covers about 20 pages and includes relatively long sections on drugs for benign breast disease and polycystic ovary syndrome, the author's definition of the CNS apparently being unusually broad.

The chapter contents prove to be a similar disaster. Instead of the promised clinical focus on dosage, pharmacodynamics, metabolism, and so forth, we get digressions on the mouse writhing test and the mouse hot plate test for analgesics, an outdated classification of depressive disorders, and an endless series of overdetailed tables on what neuroleptic compounds do or don't do to apomorphine-induced stereotypy and spiperone binding in rats. The final chapter, a superficial run-through of "Drugs of Ethno-Origin," is never convincingly related to the putative goal of the book. Pronouncements in some chapters (e.g., that chloral hydrate is "obsolete" or that the neurologic symptoms of acute lithium intoxication "gradually develop over months or even years") make the reader question the authors' competence. The writing styles range from repetitious wandering to excruciating circumstantiality. Where was the editor during all of this?

As for physical characteristics, the binding is sturdy and the typography drab. The index is woefully incomplete, but it hardly matters. What is there to do about a poorly organized, poorly written, and poorly edited book that fails dismally to achieve its stated purpose? Fortunately, because of the outrageous publisher's price, few people are likely to make the mistake of buying it.

#### **REFERENCES**

- Baldessarini RJ: Chemotherapy in Psychiatry, revised ed. Cambridge, Harvard University Press, 1985
- Hollister LE: Clinical Pharmacology of Psychotherapeutic Drugs, 2nd ed. New York, Churchill Livingstone, 1983

J. DEVANCE HAMILTON, M.D. Houston, Tex.

Psychopharmacology of Sexual Disorders, edited by Mark Segal. London, John Libbey, 1985, 167 pp., \$46.00.

Although it is encouraging to learn that basic scientists and clinicians throughout Europe and America are turning their attention to the brain mechanisms underlying sexual behavior, it is disappointing to experience once again the publication lag time. This densely written volume is based on expanded reports given at an international conference held early in the 1980s. Both animal and human data are used to explicate the action and interaction of dopamine, serotonin, endorphins, and hormones at a subcortical level, primarily the medial preoptic-anterior hypothalamic region and its projections. The book is more concerned with neuroendocrine mechanisms than neuroanatomical relationships. Most of the papers are well referenced and geared to fellow investigators.

Basic and clinical science come together most productively in this volume when opiate addiction is discussed. Experiments with opiates and opiate antagonists not only confirm centuries-old observations about the sexual debilitation of opiate addicts but also raise some important questions about the role of the endogenous opiates in physiological events such as the refractory period and the fluctuation of sexual desire.

Readers are reminded of the limitations of the data on the sexual side effects of commonly used and abused drugs and of the uncertainty of the mechanisms underlying impotence. The sexually stimulating activity of dopaminergic compounds such as apomorphine, bromocriptine, and L-dopa is discussed from vantage points that will be novel for most clinicians. Although the material is not yet highly useful to psychiatrists, this volume is an early step in the effort to elucidate the neurochemistry of sexual function and its problems. The authors are mindful that cortical and peripheral mechanisms are also involved. Since the publication of this volume, the use of papavarine and medroxyprogesterone for sexual disorders has come into practice. The absence of discussion of these topics already dates this book.

STEPHEN B. LEVINE, M.D. Cleveland, Ohio

Clinical and Pharmacological Studies in Psychiatric Disorders, edited by Graham D. Burrows, Trevor R. Norman, and Lorraine Dennerstein. London, John Libbey, 1985, 388 pp., \$46.00.

This book is a compendium of selected papers from the 14th congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) held in Florence, Italy, on June 19–23, 1984. The editors have reviewed the conference proceedings and selected 61 presentations from the free communications sessions for inclusion in the book. Abstracts of the plenary and symposium presentations have been published as a supplement to Clinical Neuropharmacology (number 1, volume 7, 1984). Clinical and Pharmacological Studies in Psychiatric Disorders is the fifth in a series entitled Biological Psychiatry in Psychiatric Disorders published by John Libbey. Some may recall that the second book in this series was similarly selected papers of the 1982 CINP meeting held in Jerusalem.

This book is organized into eight sections that range across topics in biological psychiatry: Affective Disorders—Pharmacological Aspects; Affective Disorders—Clinical Studies; Anxiety, Panic Disorders and Stress; Psycho-Neuroendocrinology; Schizophrenia; Basic Neuropharmacology; Alzheimer's Disease; and Psychogeriatrics. Each section consists of six to nine papers of approximately 1,000 to 5,000 words in length. The majority of the papers describe original investigations by the authors. However, interspersed with the data-based presentations are occasional theoretical articles, such as "Neurotransmitters in Anxiety: A Reappraisal" by Hoehn-Saric; topical reviews such as "Affective Disorders in the Elderly: Treatment Considerations" by Georgotas and McCue; and even a "how-to" paper, "Organizing a Stress Clinic" by Wheatley.

The section on pharmacological studies of affective disorders focuses on adrenergic receptor function, and the section on clinical studies of affective disorders describes diverse pharmacological treatments of mood disorders, including new tricyclic and monoamine oxidase inhibitor antidepressants and calcium channel blockers. Of particular interest is a report of sulpiride's antidepressant and anxiolytic effects by Standish-Barry et al. The sections on anxiety disorders and schizophrenia predominantly comprise biological assess-

ment studies and pharmacological trials. A report by Bondy et al. describing increased  $^3H$ -spiperone binding in lymphocyctes of schizophrenic patients and family members was intriguing. The section on psychoneuroendocrinology is focused almost entirely on studies of the dexamethasone suppression test (DST), which is not surprising because the conference took place at a zenith in research activity on the DST. The section on basic neuropharmacology includes studies of serotonergic, adrenergic, and  $\gamma$ -aminobutyric acid (GABA) receptor function. The section on Alzheimer's disease includes nine studies evenly apportioned among neurochemistry, neuropathology, and pharmacological treatment. The section on psychogeriatrics comprises mainly reports of treatment trials.

On the whole, the papers are brief and concisely written in the style of scientific reports to a professional journal. In fact, with the variety of authorship and topics of the different articles, the book reads much like a scientific journal with the articles abridged. This feature of the book may work against it in terms of its uneven nature and, at times, dryness of the writing style. On the other hand, this book is not really meant to be read in its entirety from beginning to end but to serve as a reference volume to readers with particular interests and/or those who wish to avail themselves of a brief sampler of "cutting-edge" research.

As invariably happens in efforts to convey the latest research activities on a large scale through the vehicle of a book, some of the material has already become dated. For example, drugs used in some of the studies (e.g., gammavinyl-GABA, a treatment for tardive dyskinesia, and BW 234U, a putative novel antipsychotic) have already fallen by the wayside. Despite this, most of the book's scientific content is relevant and current. Considering the logistical enormity of the editors' task—the book has 229 contributors from 13 countries—I think the editors have succeeded in bringing a varied and interesting portion of the CINP meeting program to a larger audience. It may not be quite the same as having been in Florence, but the book's price is certainly more affordable.

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#### SUBSTANCE ABUSE

The Substance Abuse Problems, vol. 2: New Issues for the 1980s, by Sidney Cohen. New York, Haworth Press, 1985, 323 pp., \$34.95; \$19.95 (paper).

I began my review of Sidney Cohen's first collection of newsletters (1) with these words:

There are three types of newsletters: those you throw away, those you read and throw away, and those you read and don't throw away.

Sidney Cohen's newsletters belong in the latter category. Since 1972 he has been turning out splendid little essays on substance abuse and, for certain, many of them, corners curling, still reside in the filing cabinets of those fortunate enough to be on the mailing list.

Undoubtedly, many still reside in filing cabinets. This second volume illustrates why: the newer essays are just as good as the older ones and sustain Dr. Cohen's reputation as the country's number 1 authority on drug abuse.

Although trained as an internist, Cohen is currently Clinical Professor of Psychiatry at the University of California, Los Angeles. The newsletters were written under the auspices of the Vista Hill Foundation. They cover an amazing range of topics: cocaine, marijuana, alcohol, the anxiolytics, caffeine, opiates, hallucinogens, prescribing practices, high-priced athletes, pain, and the autoimmune deficiency syndrome (AIDS).

The nicest thing about Cohen, aside from his wit and lucidity, is his laid-backness. The United States is experiencing one of its recurring cycles of drug hysteria. The President calls for a "national crusade" against drug abuse, saying that drug abuse is a "repudiation of everything America is" and calling for a "drug-free" country. He wants everybody in the government (presumably even Supreme Court Justices) to have urine tests.

There is none of this language in Cohen's book. He has no illusions about a drug-free country. Drugs have always been with us and always will be. But the drugs change with time, and the rate of change is increasing. He finds this remarkable: "It is not that we abandon the original drugs. New ones are overlaid and used jointly or sequentially with the old. Meanwhile, our basic potion, alcohol, underlies them all."

Cohen considers multihabituation—better known as polydrug abuse—a fairly new phenomenon: "Although speedballs were known in bygone days, most career drug abusers were true to one substance, and were identified after their agent of choice as potheads, hopheads, rumheads, pillheads and cokeheads. Now garbage heads must be added to the list."

Also new are rapid drug delivery systems: "Until recently, the taboo against using a needle to introduce substances into a vein was strong, and some still faint at the sight of an approaching injection. That taboo has been breached by hundreds of thousands of people from every social class in recent years."

Inhaling fumes is even more rapid. Who knows? Before long junkies may be injecting chemicals directly into the brain. "Beyond that," Cohen speculates, "implanted electrodes in the reward areas loom for those who want pleasure now and on demand."

Controlling the supply of drugs is no solution: "Now we have to cope with designer drugs which are not yet illegal. By the time they are declared illegal, a new series of related drugs . . . [will be] ready for sale."

Nor is he optimistic about education: "It may seem odd on the face of it that telling people of the dire consequences that will result from the continued use of a drug ordinarily does not affect the drug-using behavior." Needed is a social revolution. Cohen is not holding his breath waiting for it.

Cohen does not mention nicotine—in this volume at least. Nor do the politicians. In Cohen's case the reason is not hypocrisy; he didn't get around to it. The politicians are hypocritical. While condemning drug abuse as a "repudiation of everything America is," President Reagan continues to support the subsidization of tobacco farming. Of all the killer drugs, tobacco overwhelmingly ranks first on the list.

Apart from this omission, Cohen's book is commendable.

#### REFERENCE

 Goodwin DW: Book review, S Cohen: The Substance Abuse Problems. Am J Psychiatry 1982; 139:376–377

DONALD W. GOODWIN, M.D. Kansas City, Kans.

The Diagnosis and Treatment of Drug and Alcohol Abuse, edited by Sidney Cohen and James F. Callahan. New York, Haworth Press, 1986, 305 pp., \$39.95.

Some physicians enjoy taking tests and find the examination process an effective way to learn. The popularity of APA's Psychiatric Knowledge and Skills Self-Assessment Program attests to that curious fact. For those of us who find examinations a pleasurable challenge, Sidney Cohen and James F. Callahan provide a bonus of 200 short-answer questions integrated into this new textbook. The questions are grouped into a pre- and posttest of 50 questions each for the diagnosis and treatment section of the text.

The book is derived from a number of monographs previously published by the National Institute on Drug Abuse (NIDA) and includes the work of seven authors. Their material has been updated and is presented in a new and convenient format. The first half of the volume consists of five chapters on the diagnosis of alcohol and drug abuse and eight on treatment, along with the multiple-choice tests. The second half is made up of three appendixes. Appendix A is a useful assessment interview guide. Appendix B offers a quick reference, with a number of charts and tables, to the diagnosis and emergency management of the various intoxication, overdose, and withdrawal syndromes. The final appendix is a compendium of information on resources for health professional training in drug and alcohol problems. This section provides an annotated list of available curricula, training manuals, films, and videocassettes. It discusses the present status of certification examinations and procedures and includes a list of relevant organizations. This resource compendium contains a great deal of detail, including the names, addresses, and telephone numbers of past and present recipients of NIDA/National Institute on Alcohol and Alcohol Abuse (NIAAA) Career Teacher grants and members of a former task force on professional education. Also within this final section is a list of educational materials that have to do with prescribing, dispensing, and administering controlled substances.

This book's great strength is its practical orientation. It does not cover theories of addiction, etiological factors, or epidemiology as separate subjects but integrates such information when it is relevant to diagnosis and treatment. It cites very few individual studies (there are usually six or fewer references per chapter), seeking instead to synthesize and apply current knowledge. Its discussions and recommendations are always concrete and specific. This specificity makes the book useful to physicians in emergency rooms, general hospitals, and office practice as well as to students and those of us who want to update our knowledge or prepare for an examination.

Unfortunately, the volume has some weaknesses as well. Its derivation from NIDA monographs may explain the relative weakness in its coverage of alcoholism treatment, specifically the postdetoxification, rehabilitation phase of treatment. The section on rehabilitation in general is divided into a chapter on pharmacotherapy and one on sociotherapy. Although the first provides an adequate discussion of the use of disulfiram in alcoholism, the latter makes no mention of the intensive inpatient and outpatient rehabilitation program model that is most widely used in the United States today. Such programs are designed for the treatment of alcoholism and related drug dependencies and often use the overall concept of "chemical dependency." They combine a relatively short-term inpatient stay, under the care of an interdisciplinary team, with long-term outpatient follow-up.

Family involvement, education about addiction, and various forms of group therapy are stressed. Self-help approaches are integrated into the program and in the long-range treatment plan. It is hard to understand why this effective and increasingly popular model was overlooked. The volume also omits any clear discussion of the role of psychiatric management and psychotherapy in the treatment of drug and alcohol abuse. The reader who might choose to use this book as a teaching text or an examination review should be aware of its incompleteness. Other sources of information will be needed to provide a balanced picture of contemporary treatment for drug and alcohol dependencies.

In spite of the book's omissions, however, it can be of value to the student and practitioner and might be a great help in preparing for the certification examination sponsored by the American Medical Society on Alcoholism and Other Drug Dependencies. It is especially recommended for those who, like me, enjoy taking tests.

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Alcoholism and Substance Abuse: Strategies for Clinical Intervention, edited by Thomas E. Bratter and Gary G. Forrest. New York, Free Press, 1985, 650 pp., \$49.00.

This volume is a collection of edited chapters dealing with the psychotherapy of alcoholism and other substance abuse disorders. Although focused on treatment issues, it discusses etiology and assessment concerns in sections leading to the main discussion of psychotherapeutic models used for substance abuse patients. Psychotherapy models covered include individual, group, psychodynamic, systems, behavioral, and self-help. Chapters on these models of psychotherapy tend to be position papers, with experts on each model presenting the theoretical reasons for their use of a particular approach in the substance abuse population.

The use of psychotherapy as a treatment modality for substance abuse patients is defended in this volume as an alternative to the "powerful psychiatric-medical establishment" model of the treatment of mental illness. Dr. Bratter, an editor and author of three chapters in this volume, has been a critic of psychiatry as a discipline that forces "punitive care, custody, and control" on mental health patients. His polemic is based on vague references to overuse of antipsychotic medication and ECT as a treatment usually "administered punitively or as a warning to the potentially disruptive." Bratter views the "American self-help residential therapeutic community" as the most effective form of substance abuse treatment.

The self-help therapeutic community is described as a confrontational approach that relies on milieu therapy to treat substance abusers with characterological disturbances. This model has developed from the original Synanon group, which Bratter describes as now moving away from the treatment of characterologically disturbed individuals with substance abuse problems to a religious commune atmosphere. Whether this confrontational approach to dealing with substance abusers with antisocial characterological problems is effective is unknown, just as rigorous treatment outcome data are missing for other theoretical psychotherapy approaches. Where data are missing, as they are for the comparative effectiveness of treatment programs in alcoholism, arguments are usually based on training models and opinion. Often the intensity and volume of the argument are

inversely proportional to the evidence supporting the argument. A number of chapters in this book are quite noisy.

This volume is introduced as one that will be "very helpful in ... [clinicians'] efforts to treat and do research on substance abusers." However, it might better be used as a reminder that we have a long way to go in understanding the natural history of substance abuse disorders and how treatment might best be structured. One might better use Vaillant's The Natural History of Alcoholism (1) or Goodwin's Alcoholism: The Facts (2) as starting points and consider that substance abuse treatment could be an epiphenomenon of natural recovery in alcoholism and other substance use disorders. Until more rigorous treatment outcome research data are available, advocates of various treatment approaches need to recognize the nonspecific benefit of any program that gives the substance abuser the opportunity and expectation for change. The intensity of arguments about specific treatment approaches might therefore be directed toward productive cooperative treatment studies benefiting both the substance abuse treatment professional and the substance abuse victim.

#### REFERENCES

- Vaillant GE: The Natural History of Alcoholism: Causes, Patterns, and Paths to Recovery. Cambridge, Harvard University Press. 1983
- Goodwin DW: Alcoholism: The Facts. New York, Oxford University Press, 1981

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#### CHILD PSYCHIATRY

Late Adolescence: Psychoanalytic Studies, edited by David Dean Brockman. New York, International Universities Press, 1985, 307 pp., \$37.50.

This new collection of essays is timely, appearing at a moment of renewed interest in understanding human development. Witness, for example, two fairly recent books, one dealing with the full range of the life cycle from earliest infancy to the late adult years (1) and the other considering developmental continuities and discontinuities (2). Investigating human development in exquisite detail is hardly new to psychoanalysis. From the start, such topics as conceptualization of early development and identification of the role of historical factors in subsequent individual development have had an important role in theoretical models and therapeutic interventions. What is new in the current efforts is the involvement of multiple perspectives, including sociology and life-span developmental theory and reflecting the recognition that several vantage points are required to advance knowledge of the human life cycle. Also new is an increased concentration on clarifying phases of adult development, which may be even more difficult to conceptualize than earlier years, given the complex intertwining of biological and social forces in the later phases of life (3).

The current volume, dealing in many ways with the transition between late adolescence and young adulthood, represents another valuable contribution to this growing literature on the contemporary life cycle. The volume concentrates on observations and insights gained from psychoanalysis. Although all of the chapters are linked with psy-

choanalytic thought, they do not convey a single narrow approach. Rather, they emphasize the important mix of theoretical frameworks that characterizes the contemporary scene. Thus, important themes in the book touch on traditional ego psychology, drive psychology, and self psychology (vicissitudes in self-esteem and self-representations). This is a commendable aspect of the book, in the light of the range of problems and patterns that must be considered in analyzing the complexities of adolescent development and transitions from this phase to adulthood.

The editor has succeeded admirably in knitting together many diverse chapters. As is often the case with such collections, the chapters vary considerably in their coherence, comprehensiveness, and clarity. I found the editor's "interventions" extremely helpful, beginning with his introductory chapter, where he thoughtfully sets the stage by reviewing many aspects of late adolescence, drawing on both psychoanalytic and nonpsychoanalytic approaches. His careful scrutiny recurs throughout the volume, as he begins each major section with an introduction that anticipates the points of convergence and contrast of the subsequent chapters. These section introductions are an excellent feature of the book. I frequently turned to them while reading a given section when puzzled or intrigued by hints of new connections among the chapters. All too often, an edited book moves from a sketchy introduction to a diffuse collection, thereby distracting the reader and probably undermining the separate chapters as they become part of this scatter. For his devoted integrations, Dr. Brockman deserves the gratitude of reader and contributor for enhancing the value of this volume.

Not surprisingly, the beginning sections of the book include developmental and theoretical considerations. Two more clinically oriented sections follow, dealing with depression and learning inhibitions. The chapters in these sections are somewhat uneven, perhaps partly as a result of the fact that two were published previously and were thus not specifically oriented to the aims of this book. Those chapters deliberately written for inclusion in *Late Adolescence* seem to "work" better.

Particularly thoughtful and interesting chapters in the first sections include Galatzer-Levy's discussion of adolescent breakdown and middle-age crises. This chapter sensitively illustrates and examines the impact of parents on adolescent development as well as the influences of adolescents on their parents' functioning. In the theoretical section, there is an excellent chapter by Richmond and Sklansy, "Structural Change in Adolescence." These authors bring together a number of writings about the development of autonomy during adolescence. In addition to Erikson's well-known contributions to this area, the authors also review the pertinent and insightful ideas of Roy Schafer on the formation of ideals and values during adolescence. Although it appeared subsequent to the publication of this book, the recent thoughtful paper on autonomy in adolescence by Steinberg and Silverberg (4) nicely illustrates how the thinking of investigators in child development can dovetail with the broad psychoanalytic ideas that are presented in this

The more diagnostically oriented sections on depression and learning inhibitions are also noteworthy. They emphasize the contributions of "self psychology" to understanding depression during adolescence. They also focus on possible misdiagnosis or "underdiagnosis" of severe difficulties that may masquerade as learning or productivity "blocks" during late adolescence.

The strongest sections of the book are the final ones, those dealing with psychoanalytic therapy and applied psychoanalysis. These chapters are especially well written and clearly focused, and they offer many provocative ideas. In "Psychoanalytic Treatment of the Young Adult: Technical and Theoretical Considerations," Jacobs uses well-selected clinical material to highlight both the difficulties and the successes in interventions with late adolescent/young adult patients. In this chapter, a number of the dilemmas that one faces in treating late adolescent and young adult patients are clearly explicated and then discussed in rich and perceptive ways. The chapter by the editor, "Focal Analysis of a College Freshman," is most interesting, describing the course of a brief period of psychoanalysis for a young undergraduate. Finally, the last section, Applications, has a wonderful essay by Ernest Wolf considering Freud's concept of adolescent creativity in terms of self psychology. This is a graceful, elegantly written chapter that sheds much light on how self psychology conceptualizations can lead to a sensitive and deeper understanding of adolescent phenomena.

On balance, this is a valuable volume for students of adolescent development, therapists who deal with various phases of adolescence, and life-span development scholars. The book has much that one can admire and treasure. I think that its contributions may be provocative and hypothesisgenerating for empirical investigators in other fields as well as enriching for those who work within psychoanalysis or other therapeutic modalities. I highly recommend this volume for investigators as well as practitioners who are currently struggling to grasp the perplexing vicissitudes of adolescent and adult development.

#### REFERENCES

- Offer D, Sabshin M (eds): Normality and the Life Cycle: A Critical Integration. New York, Basic Books, 1984
- Emde R, Harmon R (eds): Continuities and Discontinuities in Development. New York, International Universities Press, 1984
- Hauser S, Kates W: Understanding adults. Psychoanalysis and Contemporary Thought 1982; 5:117–146
- Steinberg L, Silverberg S: The vicissitudes of autonomy in early adolescence. Child Dev 1986; 57:841-851

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Children on Medication, vol. I: Hyperactivity, Learning Disabilities, and Mental Retardation, by Kenneth D. Gadow. San Diego, College-Hill Press, 1986, 251 pp., \$17.95 (paper).

Children on Medication, vol. II: Epilepsy, Emotional Disturbance, and Adolescent Disorders, by Kenneth D. Gadow. San Diego, College-Hill Press, 1986, 249 pp., \$17.95 (paper).

These two companion volumes represent a psychopharmacology text written for teachers, parents, and child-care professionals without a background in psychopharmacology. Pediatric psychopharmacology requires effective interdisciplinary collaboration, and this collaboration is immeasurably enhanced by a shared understanding of the concepts, facts, and operating principles of pharmacotherapy. A prescribing physician who has tried to talk with school personnel after they have consulted the *Physicians*'

Desk Reference will quickly grasp the need for this book. I know of no other text that serves a similar purpose. Dr. Gadow stresses that Children on Medication is not a do-it-yourself manual of psychopharmacology. On the other hand, the studies of Dr. Gadow and his colleagues on the medications prescribed within schools and institutions (1, 2) highlight the need for adequate monitoring of psychotropic medications in these settings. In taking a step toward fostering interdisciplinary communication, Children on Medication addresses this larger social concern.

These volumes are organized around the classification of childhood problems used by special educators, the medical diagnoses and target symptoms for which psychotropic medications are indicated, and the special situations of young children and adolescents who may require pharmacotherapy. Each volume opens with an introductory chapter entitled "Fundamental Concepts of Pharmacotherapy," about which I have more comments later in this review.

There is an extensive and generally excellent chapter discussing the issues involved in treating hyperactive children. It is current and very readable. A long chapter on learning disabilities follows. Since there is no recognized pharmacotherapy for this heterogeneous group of conditions, I found the level of detail excessive and ultimately confusing. The author should have been more concise. The chapters on children with mental retardation and seizure disorders are well written and informative, and the chapter entitled "Emotional Disturbance" (a rubric of special education) touches briefly on the issues of medication treatment for infantile autism, childhood schizophrenia, conduct disorders, and childhood depression. Finally, there is a chapter on the pharmacotherapy of young children and adolescents and one on other disorders—cerebral palsy, enuresis, school phobia, and Tourette's disorder. Excellent bibliographies and appendixes support the text, making the material covered accessible and of immediate practical value.

Writing a pediatric psychopharmacology textbook must be a little like forging a consensus at the United Nations—it leaves no one completely satisfied. With this caveat in mind I will present some of the differences I have with this book. My most significant objection is the absence within the introductory chapters to each volume of a specific discussion of the personal, social, ethical, and legal dimensions of pharmacotherapy.

These dimensions, and our conceptualizations of them, are as real and as fundamental as any dose-response curve or serum half-life determination. They include an appreciation of the meanings that taking a medication may have for a child and an understanding of what constitutes informed consent and who may consent to treatment. They also include an understanding of the kinds of clinical trials by which the efficacy and side effects of medications are scientifically established and the processes by which the Food and Drug Administration approves medications for specific purposes. An understanding of these issues is often central to much that is therapeutic in pharmacotherapy, and such an understanding is especially relevant for this audience.

Secondarily, I feel the text might have placed more emphasis on the issue of sustained attention as a central mechanism for the therapeutic effects of psychostimulants. In discussing neuroleptics it would have been helpful to distinguish withdrawal dyskinesias from dyskinesias that persist chronically after medications are withdrawn. This distinction is worthwhile because the significance of withdrawal dyskinesias in children is not well understood. Finally, the

organization of the book could have been improved by specific chapters on the major classes of psychotropic drugs. Because this information is scattered throughout the text, there is a certain amount of redundancy.

Despite these problems, the author writes sensitively about the dilemmas of physicians, parents, and school personnel who must confront many clinical uncertainties and a lack of adequate scientific data in making decisions regarding pharmacotherapy. I can recommend this text as a starting point for discussion of pharmacotherapy with the audience for whom it is intended. I hope that future editions of Children on Medication will make its realization as praiseworthy as its purpose.

#### REFERENCES

1. Gadow KD: Prevalence of drug treatment for hyperactivity and other childhood behavior disorders, in Psychosocial Aspects of Drug Treatment for Hyperactivity, Edited by Gadow KD, Loney J. Boulder, Westview Press, 1981

2. Gadow KD, Kalachnik J: Prevalence and pattern of drug treatment for behavior and seizure disorders of TMR students. Am J

Ment Defic 1981; 85:588-595

ANTHONY H. JACKSON, M.D. Needham, Mass.

Emerging Issues in Child Psychiatry and the Law, edited by Diane H. Schetky, M.D., and Elissa P. Benedek, M.D. New York, Brunner/Mazel, 1985, 346 pp., \$37.50.

The sequel to a hit movie has the same characters and plot and is often given a Roman numeral, such as Rocky IV. Like a movie, books have sequels. The publicity about this book as a sequel prompts me to consider whether it fits that pattern. This book follows Child Psychiatry and the Law (1), published in 1980. The response to that book was gratifying; it sold more than 20,000 copies, a very good sale for a professional book, and it prompted this book. In the earlier book, the same editors brought together 16 authors to produce 18 chapters of high quality. In the sequel, the editors, with 26 contributors, give us 22 chapters. Only one contributor is a repeater—Dr. Lenore C. Terr, the author of two chapters in the first book, one on the child as a witness and another on personal injury to children, and one in the second book, also on the child as a witness.

The first book had chapters on the juvenile court system, court evaluation, the expert witness, child custody, neglect, adoption, status offenders, delinquents, juvenile murderers, civil commitment, psychic trauma, personal injury to children, competency, criminal responsibility, and the child as a witness. This book is divided into five sections, each of which is devoted to a different topic. The sections are cohesive, but the book as a whole suffers the vulnerability of a multiauthored book—to wit, a lack of flow and continuity. Section one, Ethics, covers children's capacity for participation in treatment decision making, refusal of treatment in childhood cancer, and organ transplants and research with children. Section two, Child Custody, considers child custody disputes, mediation, joint custody, father custody, lesbian mothers and gay fathers, grandparent visitation, and sexual abuse. Section three, The Juvenile Offender, deals with the juvenile justice system, waiver of juveniles to adult court, and treatment alternatives in juvenile justice programs. Section four, Special Issues, covers legal issues and the schools, psychiatric commitment of children and adolescents, psychiatric approaches to cults, role models for violence, and psychiatric interventions with children traumatized by violence. Section five, Emerging Issues, covers the baby as a witness, areas of litigation for children, and the interface of law and psychiatry. Except for the last 15 pages, most of the "emerging issues" discussed in this book emerged long ago.

All in all, I liked this book, but I liked the earlier one even more. The first book was more like a textbook in that it covered basic, fundamental issues in child psychiatry and the law. It encompassed those areas most likely to be encountered in the practice of child psychiatry or psychology. The sequel is, more or less, like a compilation of journal articles. They are scholarly but, as in the case of movies, the first will likely find wider appeal. Ian Fleming's James Bond series consisted of rewrites of the same story, but they met with universal popularity. That was because, as psychiatrists would say, they dealt with unresolved oedipal conflicts. That's not to be expected when discussing child psychiatry

and the law.

#### REFERENCE

1. Schetky DH, Benedek EP (eds): Child Psychiatry and the Law. New York, Brunner/Mazel, 1980

> RALPH SLOVENKO, LL.B., PH.D. Detroit, Mich.

Reprints of Book Forum reviews are not available.

### Letters to the Editor

#### Depot Neuroleptics for Acutely Psychotic Patients

SIR: The staff of our acute intensive care unit is often confronted with acutely psychotic patients, hospitalized against their will, who adamantly refuse medications. We immediately initiate the legal "de novo" proceedings required by the Commonwealth of Kentucky statute for medicating such patients against their will. Those proceedings are quite lengthy, however-1 week to 10 days. During that period of time, the patient's behavior is carefully monitored to assess imminence of danger to self or others. If there is such a danger, the treatment team organizes a show of force to administer medication in compliance with the emergency provision of the law. We have had good results in administering fluphenazine decanoate, 50-75 mg, or haloperidol decanoate, 100-200 mg, instead of the hydrochloride solutions and placing the patient in restraints for a few hours. The treatment team has learned to expect and accept that under the worst of circumstances, the patient's acute symptoms will not abate immediately but will do so in a few days. This considerably lessens the staff members' level of anxiety. They are also relieved not to have to approach the patient repeatedly with offers of medication that are rejected with increasing agitation. We have often noted that the "magic" of the injection has a profoundly therapeutic effect on patients—much beyond what would be expected from the pharmacokinetics of the drugs—and that their symptoms are controlled much more rapidly than one would expect. Patients are often unconsciously relieved to see that outside control is available, and this relieves their sense of turmoil. They often start accepting supplemental oral doses of medication without further ado.

We are using this method selectively with patients who are well known to us, not only in terms of their acting out potential and usual course in the hospital but also in terms of their dose tolerance and propensity to develop side effects. If a patient has a history of extrapyramidal reactions, antiparkinsonian medication is administered prophylactically in conjunction with the depot neuroleptic injection. For patients who are not as well known, we essentially follow the same procedure but we give lower doses, such as 12.5 mg of fluphenazine or 50 mg of haloperidol decanoate.

DANIELLE M. TURNS, M.D. RAYMOND PARY, M.D. CARMELITA R. TOBIAS, M.D. WILLIAM A. JAMES, M.D. Louisville, Ky.

# Propranolol as Adjunct to Clonidine in Opiate Detoxification

SIR: Akathisia is a syndrome characterized by involuntary motor restlessness, pacing, inability to sit still, fidgeting, chewing, and leg or arm movements (1). It is most commonly a side effect of neuroleptic medication and responds to

treatment with propranolol (2). We encountered symptoms resembling those of akathisia in four patients undergoing clonidine detoxification for opiate dependency. All four patients responded to propranolol at doses of 20–40 mg/day. Propranolol was not given if a patient's systolic blood pressure was less than 90 mm Hg, diastolic blood pressure was less than 60 mm Hg, or pulse rate was less than 60 beats per minute.

Mr. A, a 30-year-old man, was taking 45–90 mg/day of methadone on admission. He underwent a difficult detoxification with clonidine, 16–18 µg/kg per day. One particular difficulty was a restlessness that he noticed most in his legs and that prevented him from sitting or lying comfortably. Propranolol, given orally in doses of 10 mg b.i.d., provided relief from the restlessness and decreased his general anxiety moderately. At no time did he become hypotensive while taking propranolol and clonidine.

Ms. B, a 25-year-old woman, had been taking "hits" of a combination of glutethimide and codeine. After a glutethimide taper she underwent a clonidine detoxification from codeine, during which she complained of restlessness and panic-like anxiety. Propranolol, 10 mg q.i.d. by mouth, relieved her anxiety and restlessness. Ms. B's lowest blood pressure was 90/54 mm Hg, and she did not experience hypotensive symptoms.

Ms. C, a 26-year-old woman, was taking 40–70 mg/day of hydromorphone and 48 mg/day of methadone on admission. After taper detoxification from sedative-hypnotics, she was detoxified from opiates with clonidine. She reported relief of all withdrawal symptoms, except for a restless anxiety, on a dose of 8–10  $\mu$ g/kg per day of clonidine. Propranolol, 10 mg b.i.d. by mouth, provided relief for this restless anxiety. Ms. C's lowest blood pressure was 90/60 mm Hg, and she had no symptoms of hypotension.

Mr. D, a 45-year-old man, underwent detoxification for benzodiazepine dependence and then detoxification from methadone. He had been taking 75 mg/day of methadone, and after a methadone taper he was started on 16 µg/kg per day of clonidine. He, like the other patients we have described, complained of restless anxiety. Propranolol, 10 mg b.i.d. by mouth, again provided symptomatic relief without producing hypotensive symptoms.

Propranolol has received previous trials as a single agent for opiate detoxification. The best of these studies (3) demonstrated that it had no significant clinical usefulness. In contrast to previous studies, however, we used propranolol as an adjunctive medication to assist clonidine detoxification. While our report must be considered preliminary, there are possible explanations for propranolol's apparent efficacy. Propranolol may bind to cerebellar  $\beta$ -adrenergic receptors or act to block postsynaptic effects of locus ceruleus firing (4,

5). We suggest that the apparent efficacy of propranolol justifies further studies, and its safety permits further research.

#### **REFERENCES**

- Klein DF, Gittelman R, Quitkin F, et al (eds): Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children. Baltimore, Williams & Wilkins, 1980
- Adler L, Ángrist B, Peselow E, ét al: Efficacy of propranolol in neuroleptic-induced akathisia. J Clin Psychopharmacol 1985; 5:164-166
- Resnick RB, Kestenbaum RS, Schwartz LK, et al: Evaluation of propranolol in opiate dependence. Arch Gen Psychiatry 1976; 33:993-997
- VanDongen PA: The central noradrenergic transmission and the locus coeruleus: a review of the data and their implications for neurotransmission and neuromodulation. Prog Neurobiol 1981; 16:117–143
- Gold MS, Rea WS: The role of endorphins in opiate addiction, opiate withdrawal, and recovery. Psychiatr Clin North Am 1983; 6:489-520

HERBERT ROEHRICH, M.D. MARK S. GOLD, M.D. Summit, N.J.

#### Abuse of Fluoxetine by a Patient With Anorexia Nervosa

SIR: Fluoxetine is a psychoactive compound currently under investigation for use as an antidepressant (1, 2). It is reported to have few side effects (3); however, isolated cases of mania have occurred during fluoxetine therapy (4, 5). Since little has been written about the effect of this drug on patients with anorexia nervosa, I would like to report a case of fluoxetine abuse by an anorexic patient.

Ms. A was a 39-year-old single woman whose history of anorexia nervosa with abuse of laxatives dated back to the age of 13. She had maintained a normal weight for the last 5 years but suffered chronic depression during this time. She had not responded to conventional treatment for depression and had eventually begun to take fluoxetine in connection with a university research program. She had not informed her prescribing physician of her anorexia nervosa. Her prescribed dose of fluoxetine was 60 mg/day.

Ms. A reported that after 10 days of fluoxetine therapy, she experienced a profound suppression of appetite. Her depression did not improve, but she continued to use the drug to promote weight loss. She later admitted that she had claimed to experience improved mood so that she could continue to obtain fluoxetine, although she actually used the drug solely for its appetite-suppressing effect. She reported that she increased her dose to 90 mg/day and eventually to 120 mg/day in the hope of maintaining appetite suppression and rapid weight loss. She lost 20 lb. in a 2-month period during this treatment.

Fluoxetine may have an appetite-suppressing effect in some individuals. Because it has few side effects, the drug could be easily abused by those seeking to lose weight. This could be quite problematic in patients with body image distortion, such as those with anorexia nervosa. There are clinical implications, since this medication may be considered as a possible treatment for binge eating in bulimia. Physicians should bear this problem in mind when treating depressed patients with fluoxetine.

#### REFERENCES

- 1. Chouinard G: A double-blind controlled clinical trial of fluoxetine and amitriptyline in the treatment of patients with major depressive disorder. J Clin Psychiatry 1985; 46(3, section 2):32-37
- Feighner J, Cohn J: Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive order. J Clin Psychiatry 1985; 46(3, section 2):20-25
- 3. Wernicke J: The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985; 46(3, section 2):59-67
- Chouinard G, Steiner W: A case of mania induced by high-dose fluoxetine treatment (letter). Am J Psychiatry 1986; 143:686
- Turner SM, Jacob RG, Beidel DC, et al: A second case of mania associated with fluoxetine (letter). Am J Psychiatry 1985; 142: 274–275

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#### Jogging and Tourette's Disorder

SIR: Tourette's disorder is a conspicuous clinical syndrome resembling familial hyperexplexia, startle epilepsy, and the "Jumping Frenchmen of Maine" phenomenon (latah, myriachit) (1), but with a different pathogenesis. Recently, Mesulam (2) described a patient with Tourette's syndrome who suffered an exacerbation after using cocaine, which illustrates the role played by central biogenic amines in the disorder, since cocaine is a drug that inhibits the presynaptic reuptake of dopamine and of norepinephrine. That case motivated this report.

A middle-aged man with a mild, not socially disabling, familial variant of Tourette's disorder noticed that when he jogged medium distances, the sensation of well-being brought about by running was accompanied by an increase in his usual stereotyped, shouting utterances. The results of neurologic and general physical examinations were otherwise normal, as were those of an EEG.

Sandyk et al. (3) demonstrated the suppression of Tourette's disorder symptoms in children by parenterally administered naloxone, an opiate antagonist. The same group of investigators later initiated an open-label trial of oral naltrexone in five children who met *DSM-III* criteria for Tourette's disorder and who were experiencing undesirable side effects from haloperidol therapy. These researchers were able to confirm by independent videotape analysis the beneficial effects of this agent in Tourette's disorder (4). These studies indicated that endorphins, independently or in conjunction with biogenic amines, play a role in the expression of this condition.

Because jogging is known to induce release of endorphins mediating exercise analgesia and "runner's high" (5), I suggest that the experience of the patient I have described further strengthens the hypothesis that these peptides play a role in Tourette's disorder.

#### REFERENCES

- Saint-Hilaire MH, Saint-Hilaire JM, Granger L: Jumping Frenchmen of Maine. Neurology 1986; 36:1269–1271
- Mesulam MM: Cocaine and Tourette's syndrome (letter). N Engl J Med 1986; 315:398
- Sandyk R, Iacono RP, Allender J: Naloxone ameliorates compulsive touching behavior and tics in Tourette's syndrome. Ann Neurol 1986; 20:437
- Sandyk R, Iacono RP, Crinnian C, et al: Effects of naltrexone in Tourette's syndrome. Ann Neurol 1986; 20:437

Appenzeller O: What makes us run? N Engl J Med 1981; 305: 578-579

DANIEL E. JACOME, M.D. Hialeah, Fla.

# Use of a Portable-Computer Program in Behavioral Treatment of Obsessive-Compulsive Disorder

SIR: We have developed a computer program, which runs on either a portable laptop-size or calculator-size computer, to assist in the behavioral treatment of patients with obsessive-compulsive disorder and associated checking rituals. Although behavioral techniques involving exposure and response prevention produce marked and lasting improvement in the majority of patients with this disorder (1–3), the most common reason for failure of treatment is noncompliance with these techniques (1). Patients with checking rituals are especially difficult to treat behaviorally because rituals are usually most frequent when the patient is alone at home (3), and consequently these patients must self-administer the behavioral treatment (2).

Microcomputers have been used to administer behavioral instructions to agoraphobic patients (paper presented by A. Ghosh and I.M. Marks at World Congress on Behavior Therapy, Washington, D.C., 1983), and a portable computer has been used successfully in the behavioral treatment of obesity (4). Thus, we speculated that use of a portable computer might enhance compliance with behavioral treatment and assist the record keeping of patients with obsessive-compulsive disorder.

To facilitate the learning process, each patient used two portable computers in sequence. The first, a laptop computer, was used initially in the home to familiarize the patient with the procedure. The second, a calculator-size computer, was substituted after the patient had become familiar with the technique; it was carried outside the home. The computer program (OC-CHECK) follows closely the behavioral instructions we give to patients in our obsessive-compulsive disorder clinic (2), and it also stores the information patients supply about the date, time, intensity, and frequency of all urges and checking rituals.

To date we have used this portable computer program with two of our patients: a 58-year-old woman with a 37-year history of obsessive-compulsive disorder and a 25year-old man with a 4-year history of the disorder. Both patients met DSM-III criteria for obsessive-compulsive disorder, both had extensive checking rituals, and both were treated pharmacologically throughout the study (tranylcypromine, 20 mg b.i.d., in the former case and phenelzine, 30 mg b.i.d., and alprazolam, 0.5 mg b.i.d., in the latter case). Medication doses remained constant throughout the period of computer use. Both patients demonstrated rapid and significant reductions to near-zero levels in checking rituals when the portable computers were added to standard behavior therapy, which had been going on for 36 months and 3 months, respectively. Reductions in checking rituals were specific to whether the patients were using the laptop computer only at home (reductions in checking only at home) or the calculator-size computer outside the home (reductions in both locations). Both patients showed increases in rituals when they did not use the computers and subsequent reductions when use of the computers was reinstated.

We are encouraged by these preliminary results indicating that a portable-computer program is accepted by patients with obsessive-compulsive disorder and can serve as an adjunct to behavioral treatment and record keeping. We offered the computer program to two other patients in our clinic, but they declined to use it. We are currently in the process of investigating the applicability and long-term effects of this type of computer-assisted behavioral treatment in a controlled trial.

#### REFERENCES

- Marks IM: Review of behavioral psychotherapy, I: obsessivecompulsive disorders. Am J Psychiatry 1981; 138:584

  –592
- 2. Baer L, Minichiello WE: Behavior therapy for obsessive-compulsive disorder, in Obsessive Compulsive Disorders: Theory and Management. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, Mass, PSG Publishing, 1986
- 3. Rachman SJ, Hodgson RJ: Obsessions and Compulsions. Englewood Cliffs, NJ, Prentice-Hall, 1980
- Burnett KF, Taylor CB, Agras WS: Ambulatory computerassisted therapy for obesity: a new frontier for behavior therapy. J Consult Clin Psychol 1985; 53:698-703

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#### Weir Mitchell and Lithium Bromide

SIR: In 1949 John Cade serendipitously discovered that lithium salts had a sedative-like action when administered to guinea pigs. Cade then gave lithium to 10 manic patients and found that their clinical condition improved (1). This landmark discovery is recognized as the first modern psychiatric use of the lithium ion. More than 70 years before Cade's work, however, the eminent Philadelphia neurologist Weir Mitchell reported the specific value of a lithium salt, lithium bromide, in the treatment of various psychiatric conditions (2, 3).

Dr. Mitchell published two reports on the therapeutic efficacy of lithium bromide. In an article published in 1870 (2), he concluded that lithium bromide was an effective antiepileptic agent. As F. Neil Johnson pointed out in *The History of Lithium Therapy* (4), some of the patients described in that short paper had what may have been depressive equivalents (e.g., referred temporal pain, headaches, ringing in the ears), which also showed a favorable response to lithium bromide.

In 1877 Dr. Mitchell published a second paper (3), which recommended lithium bromide for the treatment of a wide variety of psychiatric conditions. I believe that this paper has been overlooked by historians of psychopharmacology. In it Dr. Mitchell presented several cases of "nervousness" that do not fit neatly into any contemporary diagnostic category. The symptoms, such as autonomic hyperactivity, emotional lability, hypervigilance, fatigue, reduced appetite, and poor sleep, seem to overlap the anxiety and affective spectra. With regard to their treatment, Dr. Mitchell wrote,

The bromides are also of the utmost utility. Among them I prefer the lithium bromide, which I introduced into medical use some years ago, and which has now stood the test of my experience as well as that of many French and German therapeutists, who have come to regard it as the most valuable of the bromides. It should be given in some simple bitter for many months, and in doses of not more than five or ten grains, thrice a day. (3)

It is particularly interesting that the higher dose which Mitchell mentioned is equivalent to 276 mg of lithium carbonate three times a day. Because such a dose might well result in lithium levels within the currently accepted therapeutic range, there is reason to believe that Dr. Mitchell's preference for the lithium salt was based on the now well-established mood-stabilizing properties of that ion.

#### REFERENCES

- 1. Cade JFJ: Lithium salts in the treatment of psychotic excitement. Med J Aust 1949; 36:349–352
- 2. Mitchell SW: On the use of bromide of lithium. Am J Med Sci 1870; 60:443-445
- Mitchell SW: Clinical lecture on nervousness in the male. Med News 1877; 35:177-184
- Johnson FN: The History of Lithium Therapy. London, MacMillan, 1984

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#### ACTH Response to Corticotropin-Releasing Hormone

SIR: Alec Roy, M.B., and associates reported normal plasma ACTH and cortisol responses to an infusion of corticotropin-releasing hormone (CRH), in association with normal basal plasma ACTH and cortisol levels, in nine drug-free schizophrenic patients (1). They concluded that "hypothalamic-pituitary-adrenal regulation is less disturbed in schizophrenia than in depression." In previous reports in the *Journal*, in fact, these investigators had observed a blunted ACTH response to CRH and elevated basal cortisol levels in depression (May 1984 issue, p. 619) and in panic disorder (July 1986 issue, p. 896). They also claimed that their data confirmed the available literature on hypothalamic-pituitary-adrenal (HPA) axis disturbances in schizophrenia, suggesting that hypercortisolism is not a prominent feature of schizophrenic patients. They cited, however, only four of the relevant studies.

The responses of ACTH and cortisol to CRH are inversely related to basal plasma cortisol levels (2). As a result, a blunted ACTH response to CRH can simply mean that the pituitary is responding normally to exogenous CRH in the presence of chronic or acute hypercortisolism, as the authors themselves acknowledged. The futility of determining derangements in the HPA axis of psychiatric patients solely on the basis of a blunted ACTH response to CRH is then obvious. Such a response could simply reflect an increased nonspecific basal cortisol secretion. Indeed, when a test of pituitary reserve, the metyrapone test, was applied to psychiatric patients, the large majority of them exhibited responses within the normal range, irrespective of diagnosis (3). This suggests an unimpaired ability of the pituitary to secrete ACTH under stimulation through the normal feedback mechanism.

Acute anxiety or agitation, which increases basal cortisol secretion, may considerably affect response to the CRH stimulation test, probably even more than is the case with other HPA axis function tests. Also, the dexamethasone suppression test (DST) has been found to be influenced by the nonspecific stress of acute psychosis and hospitalization. Of 15 unmedicated chronic schizophrenic patients with acute exacerbations and severe agitation, 11 failed to suppress cortisol secretion after dexamethasone administration (4). Their baseline cortisol levels were in the high range. The

results of that study have recently been confirmed by a similar investigation (5).

The last 5 years have witnessed the decline and fall of the myth of the DST's specificity for melancholia (3, 6). Attributing biological specificity to a blunted ACTH response to CRH does not appear to be justified by the available data.

#### REFERENCES

- Roy A, Pickar D, Doran A, et al: The corticotropin-releasing hormone stimulation test in chronic schizophrenia. Am J Psychiatry 1986; 143:1393–1397
- 2. Hermus ARMM, Pieters GFFM, Smals AGH, et al: Plasma adrenocorticotropin, cortisol, and aldosterone responses to corticotropin-releasing factor: modulatory effect of basal cortisol levels. J Clin Endocrinol Metab 1984; 58:187–191
- Fava GA, Sonino N: Hypothalamic-pituitary-adrenal axis disturbances in depression: a discussion of recent studies. IRCS Medical Science 1986; 14:1058–1061
- Herz MI, Fava GA, Molnar G, et al: The dexamethasone suppression test in newly hospitalized schizophrenic patients. Am J Psychiatry 1985; 142:127-129
- 5. Wik G, Wiesel FA, Eneroth P, et al: Dexamethasone suppression test in schizophrenic patients before and during neuroleptic treatment. Acta Psychiatr Scand 1986; 74:161–167
- Berger M, Pirke KM, Doerr P, et al: The limited utility of the dexamethasone suppression test for the diagnostic process in psychiatry. Br J Psychiatry 1984; 145:372–382

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#### Extreme Haircutting and Psychosis

SIR: We have recently had the opportunity to observe several patients on an acute inpatient psychiatric unit who had cut their hair or shaved their heads before admission. Intrigued by this behavior, we gathered the records of all patients with similar behavior whose names could be recalled by the nursing staff. We were able to document this behavior in eight patients, five of whom fulfilled *DSM-III* criteria for chronic schizophrenia—three with the paranoid and two with the undifferentiated subtype. Three other patients had a bipolar affective disorder according to *DSM-III* criteria and had cut their hair during the manic phase. Five cases are presented here.

Mr. A, a 34-year-old white man with chronic paranoid schizophrenia, reported feeling "very bad" about himself and had self-destructive thoughts that were alleviated when he shaved his head. He reported having shaved his head 6 months earlier for similar reasons.

Mr. B, a 38-year-old white man with chronic paranoid schizophrenia, had shaved his head during this first psychotic episode. He reported that the more hair he cut, the clearer his senses became. Feeling elated, he had a barber cut off all his hair.

Ms. C, a 44-year-old white woman with a bipolar affective disorder, reported cutting off all her hair on three occasions outside the hospital during manic episodes. She also had a history of wrist cutting.

Ms. D, a 22-year-old white woman with an atypical bipolar affective disorder, cut off her hair with scissors as an "offering to her doctors" during one of her admissions.

She responded to treatment, but after discharge she relapsed and again cut off all her hair.

Mr. E, a 25-year-old white man with chronic paranoid schizophrenia, had repeatedly cut his hair very short and shaved his body hair. He said that this was done in response to a voice commanding him to change his sex.

We were unable to find any documentation of extreme haircutting as a psychiatric symptom. In our eight cases, it appeared to be a manifestation of psychosis during the course of a schizophrenic or bipolar illness and so is not a specific sign. The haircutting was done for a variety of reasons. It may have been a mild form of self-mutilation in the cases of Mr. A and Ms. C. Mr. E apparently cut his hair and shaved his body in response to an auditory command hallucination; Mr. B and Ms. D apparently cut their hair in response to a delusional perception in which the act was viewed as pleasurable or necessary. We do not know why the other patients cut their hair.

Haircutting has been explained psychodynamically, and the cutting off or losing of hair has been regarded as an expression of castration (1). Berg (2) described conventional behaviors involving hair—for example, daily hair brushing, periodic haircutting, and particularly a daily shave for men—as a substitutive expression of sexual conflict, conspicuously at the genital level but with the usual contribution from the pregenital component instincts. In at least one of the patients, Mr. E, the haircutting had an obviously sexual significance.

Whatever the motivation for this unusual behavior, it is clear that it may accompany relapse. Because haircutting is not life threatening, it may be overlooked or undocumented unless it is extreme, such as head shaving. In some cases, haircutting may precede more florid psychotic symptoms, so clinicians should be alert to this symptom.

#### REFERENCES

- 1. Sperling M: The use of hair as a bisexual symbol. Psychoanal Rev 1954; 41:363–365
- 2. Berg C: The unconscious significance of hair. Int J Psychoanal 1936; 17:73–88

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#### Neuroscience and Psychiatry

SIR: In the article "Neuroscience and Psychiatry: Marriage or Coexistence" (1), Herbert Pardes, M.D., thoughtfully examined the relationship between the current revolution in the neurosciences and psychiatry. He argued that neuroscientific advancements will strengthen psychiatry and that biology will integrate with psychology. He wrote, "In answer to the question, Are neuroscience and psychologically based psychiatry reconcilable?, I submit that they are increasingly and that their reconciliation is one of the cornerstones of the field." And perhaps this is true. However, as we attempt to predict how the neurosciences will affect psychiatry, it is useful to look at other ways, both old and new, of viewing the interaction between mind and body.

To those who study the relationship between body and mind, Dr. Pardes and most modern neuroscientists would be

labeled "reductive materialists"; that is, they believe that mental states are physical states of the brain and that our present psychological theories will be modified and expanded to someday explain the complex steps from neurochemistry to "thoughts," "beliefs," and behavior (2).

Dr. Pardes' view is in sharp contrast to the long-held theory of dualism, first proposed by Descartes, in which the mind and body were considered to operate in different realms and be hardly related (3). Descartes believed that the mind influenced the body only in the pineal gland. As we have come to understand more about the workings of the brain, this theory has been largely abandoned.

There is also the well-known school of philosophical behaviorism, in which "the mind" is understood strictly in terms of observable behavior; that is, any statement about a mental state or thought can be better understood in terms of an observable behavior that would result from having such a thought or mental state (4).

Another theory of mind-body interaction widely held among contemporary philosophers and researchers in artificial intelligence is functionalism. This school holds that there are more ways than one for nature, and perhaps even man, to put together a thinking creature. Thoughts are not understood strictly in terms of neurons but, instead, in terms of functional states that might correspond to neurons, or computer circuits, or whatever else might be able to "think."

Last, there is the school of eliminative materialists, who believe that as we advance with neuroscientific knowledge, we will be forced to radically revise our present psychological theories. They argue that in other areas (physics, astronomy, biology) we have had conceptual revolutions as knowledge in the field advanced (5). So too, they argue, we will have to replace "modern" psychology with a conceptually new psychology based on neuroscience (6). It is this school that would argue most strongly against Dr. Pardes' vision of a harmonious blending of neuroscience and present-day psychologically based psychiatry.

Peaceful blending, radical revolution, or mutual coexistence—which will it be? Whichever path it takes, the field of psychiatry will be growing and changing for the better as our knowledge of the brain advances.

#### REFERENCES

- 1. Pardes H: Neuroscience and psychiatry: marriage or coexistence? Am J Psychiatry 1986; 143:1205–1212
- Churchland PM: Matter and Consciousness. Cambridge, Mass, MIT Press, 1984
- Descartes R: Meditation II, in The Meditations. Edited by Haldane ES, Ross GRT. Cambridge, England, Cambridge University Press, 1972
- 4. Ryle G: The Concept of Mind. London, Hutchinson, 1949
- Kuhn TS: The Structure of Scientific Revolutions. Chicago, University of Chicago Press, 1962
- Rorty R: In defense of eliminative materialism, in Materialism and the Mind-Body Problem. Edited by Rosenthal DM. Englewood Cliffs, NJ, Prentice-Hall, 1971

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#### Psychotic Reaction to an Insect Repellent

SIR: Because of its potential clinical importance for psychiatrists, we should like to call your readers' attention to our report (1) of a patient who developed an apparent psychotic reaction to the topical application of N,N-diethyl-

m-toluamide (deet), the active ingredient in most topical insect repellents.

Mr. A, a 30-year-old married employed man, self-treated a rash with daily applications of a 70% solution of deet, followed by heat lamp exposure, for 2 weeks. He then developed an acute manic-like psychosis with grandiose delusions and aggressivity and required hospitalization. In 6 days his psychosis had cleared, after only 15 mg of haloperidol the first day; 3 months later he was working steadily, without a recurrence of symptoms. Deet was found in his urine 12 days after the last application.

Since our report, a second case of hallucinations in an adult after frequent applications of deet was reported by Edwards and Johnson at the December 1986 midyear clinical meeting of the American Society of Hospital Pathologists. These may be the first reports of toxic psychoses induced by deet in adults. Because of its widespread use, deet should be suspected in other atypical psychoses. This may be of particular interest to military psychiatrists because of the prolonged use of deet by servicemen in hot climates.

#### REFERENCE

 Snyder JW, Poe RO, Stubbins JF, et al: Acute manic psychosis following the dermal application of N,N-diethyl-m-toluamide (DEET) in an adult. J Toxicol Clin Toxicol 1986; 24:429–439

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#### Neuroleptic Malignant Syndrome: Facts and Controversies

SIR: The editorial on neuroleptic malignant syndrome by David E. Sternberg, M.D. (1), was timely. Although our understanding of this iatrogenic entity remains patchy at the moment, the author made certain controversial statements in the editorial.

Dr. Sternberg maintained that the syndrome is more frequent with high-potency neuroleptics; however, such a conclusion is likely to be premature, as this apparent increased prevalence may be a reflection of the prescribing practices of clinicians (2). Moreover, neuroleptic malignant syndrome has been reported in association with nonneuroleptic drugs also (2, 3), a fact that seems to have been ignored in the editorial. In an extensive literature search, my colleagues and I identified a series of 14 cases in which the syndrome occurred in association with nonneuroleptic agents. However, all of these drugs affected the dopaminer-gic system in one way or another.

Dr. Sternberg suggested that neuroleptic malignant syndrome may be more prevalent in nonschizophrenic psychiatric illnesses. In a recently published review of 120 patients, 60 patients (50%) had a diagnosis of schizophrenia (3). In another review also, 50% of the patients had schizophrenic illness (2). Apart from organic brain syndrome, neuroleptic malignant syndrome has been found not to be correlated with a concurrent physical disease (3). It has been suggested that the distribution of psychiatric diagnoses of patients with neuroleptic malignant syndrome corresponds more or less to

the usual distribution of diagnoses of patients treated with neuroleptics (3).

Although I agree that the syndrome is probably missed in some patients and is often unrecognized, I feel that published case reports should be thoroughly scrutinized before they are accepted as episodes of neuroleptic malignant syndrome. Information seems to be sketchy and limited in many case reports (2, 3), leading to doubts about the diagnosis.

Dr. Sternberg said that treatment should be continued for at least a week after symptomatic improvement and longer if the syndrome is secondary to administration of depot neuroleptics. Although this may be followed as a general guideline, exceptions do occur. Because of the greatly extended half-life of depot neuroleptics, significantly elevated blood levels of these drugs remain for weeks (2). In one case report (4), an abnormally long duration of neuroleptic malignant syndrome following administration of oral neuroleptics was seen. In this case the syndrome persisted for 3 weeks after cessation of haloperidol, and the patient relapsed after a 17-day course of amantadine. Treatment was continued for another 5 months. Relapse may occur with early discontinuation of treatment (5).

I agree, however, with the overall observation that greater consideration of the diagnosis and thorough documentation will be helpful in reducing the serious consequences of this potentially fatal syndrome.

#### REFERENCES

- Sternberg DE: Neuroleptic malignant syndrome: the pendulum swings (editorial). Am J Psychiatry 1986; 143:1273–1275
- Levenson JL: Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142:1137–1145
- 3. Shalev A, Munitz H: The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986; 73:337–347
- Woo J, Teoh R, Vallence-Owen J: Neuroleptic malignant syndrome successfully treated with amantadine. Postgrad Med J 1986; 62:809–810
- Hamburg P, Weilburg JB, Cassem NH, et al: Relapse of neuroleptic malignant syndrome with early discontinuation of amantadine therapy. Compr Psychiatry 1986; 27:272–275

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#### Dr. Sternberg Replies

SIR: Dr. Adityanjee questions whether the administration of high-potency neuroleptics is associated with an especially high frequency of neuroleptic malignant syndrome, attributing this association, instead, to prescribing practices. Although the frequent association of neuroleptic malignant syndrome with high-potency neuroleptics may indeed be secondary to some third factor that is related to such medications—be it the frequency with which these drugs are prescribed, the higher dose equivalencies in which they tend to be given, or the tendency for these drugs to be prescribed when the dose is going to be rapidly increased—nevertheless, it has remained true across many studies that high-potency neuroleptics were more commonly used in patients who went on to develop neuroleptic malignant syndrome. Thus, Levenson (1) reported that 86% of the patients in his review had received either haloperidol or fluphenazine, and Shalev and Munitz (2) found that these two drugs appeared to be the offending agent in 56 of 81 cases (69%) of neuroleptic malignant syndrome that were seemingly due to one drug.

Whether the prevalence of neuroleptic malignant syndrome is higher in nonschizophrenic patients remains uncertain. A number of reviews suggest that neuroleptic malignant syndrome is more common in patients receiving neuroleptics for diagnoses other than schizophrenia (3, 4). Moreover, Dr. Adityanjee presupposes that schizophrenic patients make up only 50% of the population of patients who are treated with neuroleptics. Is there evidence that this is in fact true?

Regarding the pharmacologic management of the syndrome, I suggested that treatment should be continued "for at least a week" following oral medication and "longer" following administration of depot neuroleptics. These are guidelines only. Recent data (2) further support the idea that, in addition to clinical parameters such as temperature, muscle tone, and state of consciousness, the level of plasma creatine phosphokinase can be used to monitor the progress of treatment, since plasma creatine phosphokinase is closely correlated with the intensity of the syndrome.

Dr. Adityanjee is correct concerning the evidence that neuroleptic malignant syndrome can develop in association with nonneuroleptics; for example, it can occur after the withdrawal of dopamine agonist drugs. I did not discuss this point because my focus was on the implications of neuroleptic malignant syndrome for clinical decisions involved in prescribing neuroleptics.

Indeed, Shalev and Munitz (2), in their recent review, reported that patients who developed neuroleptic malignant syndrome tended to receive antipsychotic drugs at a relatively rapid "loading" rate, the average of which was the equivalent of adding 500-700 mg of chlorpromazine each day. Their finding provides yet another argument for "swinging the pendulum" away from the previously common clinical practice of very aggressive high-potency neuroleptic treatment (i.e., initiating treatment with very high doses or rapid acceleration of the dose: "neuroleptic digitalization") (5). The association between neuroleptic malignant syndrome and rapid increases in neuroleptic doses that Shalev and Munitz reported provides additional support for more judicious neuroleptic dosing, for study of the efficacy of low doses, and for considering the addition of nonneuroleptics (e.g., benzodiazepines) when seeking a sedative to control psychotic agitation.

#### REFERENCES

- Levenson JL: Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142:1137–1145
- Shalev A, Munitz H: The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986; 73:337– 347
- Muller PS: Neuroleptic malignant syndrome. Psychosomatics 1985; 26:654–662
- Guze BH, Baxter LR: Current concepts: neuroleptic malignant syndrome. N Engl J Med 1985; 313:163–166
- 5. Anderson WH, Kuehnle JC, Catanzano DM: Rapid treatment of acute psychosis. Am J Psychiatry 1976; 133:1076-1078

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#### Symptoms of Neuroleptic Malignant Syndrome

SIR: The article by Gerard Addonizio, M.D., and associates (1) on the neuroleptic malignant syndrome has several flaws that make it unconvincing. The first problem is the definition of "elevated temperature." A temperature of 99°F (37.2°C) is considered normal in all areas of medicine if there

has been a previous normal basal temperature. The normal variation during the day is 1.4°C, and physical activity elevates body temperature as well (2). Thus, the criteria proposed by Dr. Addonizio and his colleagues allow for a normal temperature in neuroleptic malignant syndrome. A second problem is the failure to eliminate muscle trauma or intramuscular injections as potential causes of elevated creatine phosphokinase levels. The report failed to record how often patients were evaluated for hypertension, for what duration of time they were diaphoretic, and on how many successive days they had a leukocytosis.

The article frankly points out that it was "not possible to determine which signs of neuroleptic malignant syndrome occurred before initiation of treatment." How, then, could the authors determine the prevalence of a drug-induced syndrome when they could not identify which aspects of the syndrome, if any, were in fact drug induced?

We believe the article is misleading. It does, however, illustrate the problems of retrospective studies as well as the difficulties in studying a poorly characterized syndrome. We believe that this study demonstrates the need for a prospective study of the prevalence of neuroleptic malignant syndrome. In such a study we hope that fever will be restored to its role as a cardinal feature.

#### REFERENCES

- Addonizio G, Susman VL, Roth SD: Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry 1986; 143:1587–1590
- Murphy PA: Temperature regulation and the pathogenesis of fever, in Principles and Practice of Infectious Diseases, 2nd ed. Edited by Mandell GL, Douglas RG, Bennett JE. New York, John Wiley & Sons, 1985

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#### Dr. Addonizio and Colleagues Reply

SIR: We find it difficult to understand how Drs. Friedman and Wagner concluded that our paper on the neuroleptic malignant syndrome was misleading when we specifically discussed the points they mention. They also seem to have missed a central point of the paper, which we repeatedly emphasized, namely, that the distinction between the neuroleptic malignant syndrome and symptoms of the neuroleptic malignant syndrome. We agree that elevated temperature is a cardinal feature of the full-blown neuroleptic malignant syndrome (1), but this may not be true with milder variants or incipient forms. As we pointed out in the paper, "Neuroleptic malignant syndrome is a continuous spectrum of physiologic reactions to neuroleptics that, in some patients, takes a severe, potentially lethal form." In fact, our own review of the literature (2) revealed that extrapyramidal side effects usually precede temperature elevation. In addition, as others have pointed out (3), the neuroleptic malignant syndrome may occur without a dramatic rise in temperature. Furthermore, six of eight patients with symptoms of the neuroleptic malignant syndrome in our series had a temperature higher than 99°F.

We agree that there can be many causes of elevated creatine phosphokinase levels, and in our article we pointed out that this elevation "may be seen in untreated patients." Regarding the duration of symptoms, our table 1 indicated

the duration of the syndrome for each patient. Furthermore, what we found striking was the concurrence of symptoms of neuroleptic malignant syndrome, not necessarily the magnitude or duration of any one symptom.

As we stated in the paper, we could not identify conclusively which symptoms were drug induced. We never claimed that we could. The point of the paper was that many patients have these symptoms, and it behooves us to identify causal relationships through "further well-controlled prospective studies." We join Drs. Friedman and Wagner in the desire for more prospective studies of neuroleptic malignant syndrome and believe that our paper helped to identify many of the issues which need to be examined.

#### REFERENCES

- Roth SD, Addonizio G, Susman VL: Diagnosing and treating neuroleptic malignant syndrome (letter). Am J Psychiatry 1986; 143:673
- Addonizio G, Susman VL, Roth SD: Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry (in press)
- 3. Kirkpatrick B, Edelsohn GA: Risk factors for the neuroleptic malignant syndrome. Psychiatr Med 1985; 2:371-381

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#### Lethal Catatonia and Neuroleptic Malignant Syndrome

SIR: I am in full agreement with the statement by Stephan C. Mann, M.D., and associates (1) that lethal catatonia still occurs, although it has become less frequent since the introduction of neuroleptic drugs. A better term for this condition is "pernicious catatonia," because not all cases are lethal if they are treated promptly with two or three ECTs within 24 hours. The syndrome used to occur most frequently during the hot season, when disturbed patients were placed in restraints, which increased their hyperthermia and led to vasomotor collapse.

My main reason for this letter is that on the basis of personal experience and the recent literature, I believe that patients with catatonic excitement and hyperthermia today are invariably taking neuroleptics and thus are given a diagnosis of neuroleptic malignant syndrome. No attempt has been made to study the differential diagnosis of lethal (pernicious) catatonia and neuroleptic malignant syndrome. It is striking that most of the patients with neuroleptic malignant syndrome who fail to respond to dantrolene are treated successfully with ECT. Although the French originators of neuroleptic drugs first described the syndrome in a patient given haloperidol, other neuroleptics are equally involved.

A third condition that should be mentioned is malignant hyperthermia. This condition has also been attributed to various drugs, including some used in anesthesia, such as succinylcholine. Franks and associates (2) reported in 1982 a patient with depression who had some features specific to malignant hyperthermia; the patient was unsuccessfully treated with dantrolene but responded to ECT. Since various psychotropic drugs have been reported to be responsible for malignant hyperthermia, the relationship of this condition to both lethal catatonia and neuroleptic malignant syndrome should be considered.

#### REFERENCES

- Mann SC, Caroff SN, Bleier HR: Lethal catatonia. Am J Psychiatry 1986; 143:1374–1381
- Franks RD, Aoueille B III, Mahowald MC, et al: ECT use for a patient with malignant hyperthermia. Am J Psychiatry 1982; 139:1065-1066

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#### Drs. Mann and Caroff Reply

SIR: We appreciate Dr. Kalinowsky's interest in our report. With respect to the increased frequency of lethal catatonia during the summer, our data, like those of Peele and Von Loetzen (1), indicate that it has a uniform seasonal distribution. Of special interest is a 1933 report by Derby (2) of 187 "manic-depressive exhaustion deaths," since manic patients, relative to patients with stupor, would seem particularly vulnerable to summer heat. Again, no seasonal variation was evident.

Dr. Kalinowsky underscores the intriguing clinical similarities between lethal catatonia, the neuroleptic malignant syndrome, and malignant hyperthermia. There is substantial evidence that neuroleptic malignant syndrome is associated with neuroleptic treatment and is distinct from "functional" lethal catatonia. The frequent onset of neuroleptic malignant syndrome shortly after the start of neuroleptic treatment, the many instances of recurrence of neuroleptic malignant syndrome upon rechallenge, and the occurrence of neuroleptic malignant syndrome in neuroleptic-treated patients with no evidence of a psychiatric disorder support this association (3). Furthermore, reports of conditions like neuroleptic malignant syndrome following treatment with dopaminedepleting agents or withdrawal from dopamine agonists and the involvement of dopamine in central heat-loss mechanisms and akinetic mutism strongly support the likelihood that antidopaminergic effects of neuroleptics could lead to neuroleptic malignant syndrome (3).

Nevertheless, some cases of neuroleptic malignant syndrome and lethal catatonia may be indistinguishable. Since neuroleptic malignant syndrome involves severe akinesia and hyperthermia, it most resembles cases of lethal catatonia that have a primarily stuporous course, rather than the more common "classic" lethal catatonia, which involves excitement before stupor. While excitement often precedes neuroleptic malignant syndrome, it is not associated with hyperthermia progressing to extreme levels as in "classic," excited lethal catatonia. Rather, in neuroleptic malignant syndrome hyperthermia first emerges with the onset of stupor. Thus, 78% of the 292 cases of lethal catatonia reviewed in our report appeared distinguishable from cases of neuroleptic malignant syndrome, primarily on the basis of well-documented extreme hyperthermia during the excited phase. However, 65 cases (22%) of the 292 appeared clinically indistinguishable from cases of neuroleptic malignant syndrome.

In our report we concluded that lethal catatonia represents a syndrome rather than a specific disease and that it may occur in association with organic disorders as well as various psychiatric conditions. From this perspective we suggested that neuroleptic malignant syndrome be viewed as a neuroleptic-induced toxic or iatrogenic form of organic lethal catatonia.

Aside from the critical measure of stopping neuroleptics,

the most frequently reported therapeutic interventions have involved the use of dantrolene and dopamine agonists. Observations regarding ECT in treating neuroleptic malignant syndrome are more limited (3). It appears that compared to its use in treating "functional" lethal catatonia, ECT may be less consistently effective in treating neuroleptic malignant syndrome. Furthermore, the occurrence of cardiac arrest in two cases of neuroleptic malignant syndrome and coma and atrial arrhythmia in single cases argue against its use as a primary intervention in neuroleptic malignant syndrome.

Malignant hyperthermia is considered a disorder of skeletal muscle in which exposure to certain inhalation anesthetics or depolarizing muscle relaxants intraoperatively leads to a marked increase of intracellular calcium, with consequent muscular rigidity and severe hyperthermia. While clinical and laboratory similarities between malignant hyperthermia and neuroleptic malignant syndrome have been reported (4), the mechanisms involved in the pathogenesis of these druginduced hyperthermias are probably different. To our knowledge, episodes of malignant hyperthermia have not been reported in patients with neuroleptic malignant syndrome, nor has sensitivity to neuroleptics or antidepressants been demonstrated in malignant hyperthermia patients.

#### REFERENCES

- Peele R, Von Loetzen IS: Phenothiazine deaths: a critical review. Am J Psychiatry 1973; 130:306–309
- Derby IM: Manic-depressive "exhaustive" deaths. Psychiatr Q 1933; 7:436–449
- Lazarus A, Mann SC, Caroff SN: The Neuroleptic Malignant Syndrome and Related Conditions. Washington, DC, American Psychiatric Press (in press)
- Caroff SN, Rosenberg H, Fletcher JE, et al: Malignant hyperthermia susceptibility in the neuroleptic malignant syndrome. Anesthesiology (in press)

STEPHAN C. MANN, M.D. STANLEY N. CAROFF, M.D. Philadelphia, Pa.

#### **Duty to Protect**

SIR: In regard to a recent article by Mark J. Mills, J.D., M.D., and associates (1) entitled "Protecting Third Parties: A Decade After Tarasoff," it is interesting to note that a recent decision in Delaware extends Tarasoff-like duties even beyond those of the Petersen decision (2).

In the case of Laird v. State of Delaware, a chronic schizophrenic patient drove his car across the highway, hitting another vehicle and killing its occupant. The patient had had numerous hospitalizations in state and Veterans Administration institutions over a period of about 10 years. There was no history of violence, the patient did not know the man whom he killed, and the crime (or accident) occurred 6 months after the patient had been discharged from the state hospital. He had been hospitalized for an acute psychotic episode, treated with antipsychotics, and discharged as nonpsychotic 2 weeks after admission. He did not return for a follow-up appointment and spent time in the ensuing 6 months taking some college courses. The court found the treating psychiatrist to be grossly negligent—for a crime against an unspecified, unforeseen victim 6 months after the patient's discharge from a state institution, with evidence of the patient's functional, nonpsychotic behavior during the period between discharge and the crime (or accident).

This seems an unfortunate decision, and one which heralds problems for those who believe that psychiatry, and particularly psychotherapy, is more akin to doctoring or religious confession than to policing and protection of the public at large.

#### REFERENCES

- Mills MJ, Sullivan G, Eth S: Protecting third parties: a decade after Tarasoff. Am J Psychiatry 1987; 144:68–74
- 2. Petersen v State, 100 Wn 2d 421, 671 P 2d 230 (Wash 1983)

DAVID E. RASKIN, M.D. Wilmington, Del.

#### Dr. Mills and Colleagues Reply

SIR: We thank Dr. Raskin for his letter and for the description of the Laird case. He states, we believe correctly, that the case extended the application of the Tarasoff doctrine "beyond" Petersen in that the court found liability although the patient 1) had no history of previous violence (or, presumably, threats of violence), 2) had not been hospitalized in the 6 months before the incident, and 3) was a voluntary outpatient who chose not to pursue follow-up treatment.

The case amply illustrates some of the difficulties courts and mental health professionals face in such factual circumstances. The primary problem, and apparently the determinative one from the court's perspective, was the fact that the patient was "judgment proof"; that is, because he was indigent and uninsured, the family of the decedent could not be directly compensated. Courts like to do justice in the case at bar, and given the choice between awarding no compensation and extending a useful doctrine to the point of dubiety, the court chose the latter course. We believe that mandatory automobile liability insurance laws with the state as the ultimate guarantor (or perhaps a no-fault system) would better compensate injured parties and the families of decedents without having to distort an otherwise reasonable doctrine. This case appears to be yet another illustration of the legal aphorism "Hard cases make bad law."

Nevertheless, although the result in Laird appears completely unreasonable (given the lack of linkage between hospitalization and the accident and the lack of a history of violence and/or threats), the Tarasoff doctrine should not be dismissed as senseless (1). We continue to believe that psychiatrists and all psychotherapists should intervene—typically with an appropriate clinical mechanism, for example, hospitalization—when patients meaningfully threaten others (2). Certainly, one of the problems with the Laird decision is that there was no threat and no history of violent behavior, and thus there was no clinical "notice" alerting the psychiatrist to the need for heightened clinical circumspection (3).

Besides wishing to affirm the intrinsic reasonableness of the *Tarasoff* doctrine, we believe it is noteworthy that a number of states have followed California in enacting laws that "immunize" psychotherapists from liability when psychotherapists endeavor to notify the intended victim and contact the police (4). Such laws allow psychotherapists to discharge their duty to protect relatively easily. Nevertheless, we continue to believe that these laws work best when, unlike the situation in California law, psychotherapists are

"immunized" when they hospitalize or civilly commit patients, not just when they notify victims and call law enforcement agencies (5).

Finally, it is important not to conflate the *Tarasoff* doctrine with an unfortunate misapplication. The *Tarasoff* doctrine did not compel the legal decision in *Laird*; instead, the court contorted the doctrine to compensate the family of the victim. We wonder whether, in the long run, justice was served.

#### REFERENCES

- Mills MJ: The so-called duty to warn: the psychotherapeutic duty to protect third parties from patients' violent acts. Behavioral Sciences and the Law 1984; 2:237–257
- 2. Appelbaum PS: Tarasoff and the clinician: problems in fulfilling the duty to protect. Am J Psychiatry 1985; 142:425-429
- Beck JC (ed): The Potentially Violent Patient and the Tarasoff Decision in Psychiatric Practice. Washington, DC, American Psychiatric Press, 1985
- California law limits liability of psychiatrists. Psychiatric News, Nov 15, 1985, pp 1, 17
- 5. Mills MJ, Sullivan G, Eth S: Protecting third parties: a decade after *Tarasoff*. Am J Psychiatry 1987; 144:68-74

MARK J. MILLS, J.D., M.D. GREER SULLIVAN, M.D. SPENCER ETH, M.D. Los Angeles, Calif.

#### The Borderline Diagnosis for Children

SIR: The retrospective diagnosis of "borderline" children by Deborah A. Greenman, M.D., and associates (1) was an interesting step. We believe the data point to another, better-validated diagnosis and thus do not support the conclusion that the syndrome of adult borderline personality disorder was "highly prevalent in a selected sample of hospitalized children." The diagnosis we refer to is aggressive conduct disorder, or, in *DSM-III* terms, conduct disorder, undersocialized aggressive. This syndrome, in contrast to the amorphous "borderline," has a clear definition, a known prevalence, clinical correlates, a typical family background, and a relatively well-defined natural history. The latter is also the childhood precursor and equivalent of antisocial personality disorder, from which most adult "borderline" patients suffer (2).

To test our hypothesis, we selected six distinguishing symptoms and applied them to a sample of children who had been admitted to the hospital for the treatment of conduct disorder (N=58); we also applied them to a group of suitable control subjects (N=33). We described this sample earlier in some detail (3). The six symptoms were delinquent behavior, assaultiveness, irritability and anger, being demanding or dependent, being argumentative and hostile, and hyperactivity. We left "psychotic thinking" out of this list because we did not know what was meant by this term beyond delusions, hallucinations, or formal thought disorder; none of these had occurred in our sample. "Splitting" was not rated in our sample for lack of a validated definition. Other symptoms failed to separate the groups at a significant level.

The six symptoms more frequently found in the "borderline" subjects of Dr. Greenman and associates had the following distribution in our conduct disorder group: 2% had three symptoms, 28% had four, 51% had five, and 19% had all six. In our control subjects the distribution was 52% with none, 29% with one, 10% with two, 7% with three, and 3% with four ( $\chi^2$ =75.2, df=6, p<.0001; Cramer's V=.96). The differences of proportion on all six items reached higher levels of statistical significance in our groups than they did in the "borderline" and "nonborderline" groups in the study by Dr. Greenman and associates.

Without access to the data of Dr. Greenman and her colleagues, we cannot apply the criteria for aggressive conduct disorder and for "borderline" to the two sets of samples and find out which criteria gave the best separation within samples. However, if the syndrome of "borderline" symptoms separated our two groups more efficiently than they separated the groups of Dr. Greenman et al., it seems to follow that the separation by presence or absence of conduct disorder is sharper than that of borderline versus nonborderline. We suggest, therefore, that "borderline" is a poor substitute for the rather well-defined syndrome of aggressive conduct disorder. Until evidence to the contrary is found, we think that "borderline" should be erased from the nomenclature of childhood disorders. Its use leads to mystification within the profession and even more so among nonpsychiatrists. Furthermore, it can be used as a pejorative label for patients who resist treatment.

#### REFERENCES

- Greenman DA, Gunderson JG, Cane M, et al: An examination of the borderline diagnosis in children. Am J Psychiatry 1986; 143: 998-1003
- Pope HG, Jonas JM, Hudson JI, et al: The validity of DSM-III borderline personality disorder. Arch Gen Psychiatry 1983; 40: 23-30
- Behar D, Stewart MA: Aggressive conduct disorder of children: the clinical history and direct observations. Acta Psychiatr Scand 1982; 65:210–220

DAVID BEHAR, M.D. Philadelphia, Pa. MARK A. STEWART, M.D. Iowa City, Iowa

#### Dr. Greenman and Associates Reply

SIR: As we have noted, the unexpectedly small number of significant differences between the borderline and nonborderline subjects in our study raises questions about the validity of the borderline diagnosis for children; but we do not agree that the data support conduct disorder, undersocialized aggressive type, as a meaningful diagnostic alternative.

Drs. Behar and Stewart looked for the presence or absence of six symptoms in a group who did and a group who did not fulfill DSM-III criteria for conduct disorder, undersocialized aggressive type. The symptoms were apparently chosen from the eight variables of the Diagnostic Interview for Borderlines-Revised and the four nondiagnostic variables that were significantly more frequent in our borderline group. Two (delinquent behavior and assaultiveness) are actual criteria for the diagnosis of conduct disorder, and a third (hyperactivity) is reported to be commonly associated with it. Two more (irritability and argumentativeness or hostile behavior) would be expected in children selected for their tendency to commit what DSM-III calls acts of "personal violence against persons or property." Therefore, although the six symptoms were significantly more common in the conduct disorder group, the selection of criteria makes the findings hard to evaluate.

Drs. Behar and Stewart view the link between antisocial

personality disorder and adult borderline personality disorder as further evidence of a link between borderline disorders and conduct disorder. The citing of the article by Pope et al. (reference 2 in their letter), however, is misleading. Pope et al. did not demonstrate that most adult borderline patients suffer from antisocial personality disorder but, rather, that there is an overlap between adult borderline personality disorder and antisocial personality disorder in men. (For women the overlap is between borderline personality disorder and histrionic personality disorder.)

The borderline child, like the borderline adult, has been described as not only angry and assaultive but also depressed and self-destructive (1) and vulnerable to transient losses of reality testing in the absence of diagnosable psychosis. Drs. Behar and Stewart did not use symptoms of depression, self-destructiveness, or impaired reality testing in their study. Their suggestion that conduct disorder is an alternative to a borderline diagnosis for children implies a different notion about the borderline child.

We were surprised by our failure to find a clearly discriminable group of patients who manifested outwardly and inwardly directed aggression, impaired reality testing in the absence of psychosis, and markedly impaired interpersonal relationships. However, we think it is too early to abandon the concept of such a disorder in childhood, particularly since it can be identified, even if it does not appear to be sufficiently specific. We wonder if there might be discriminable subgroups within what may indeed be an overly broad and perhaps even "amorphous" syndrome. For example, perhaps certain kinds of male patients with conduct disorder later develop characteristics of both borderline and antisocial personality disorder. We hope to look at this possibility in our follow-up study of the original sample.

#### REFERENCE

 Pfeffer CR, Plutchik R, Mizruchi MS: Suicidal and assaultive behavior in children: classification, measurement, and interrelations. Am J Psychiatry 1983; 140:154–157

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#### Usefulness of the Dexamethasone Suppression Test

SIR: I heartily concur with the conclusion of Eric D. Peselow, M.D., and associates (1) that the dexamethasone suppression test (DST) has little usefulness in monitoring long-term outcome in affective disorders. Further, there seems little reason to order the DST at all.

While two-thirds of patients with depressive disorder will have nonsuppression on the DST (2), clinicians must still treat all patients, whether their serum cortisol levels are suppressed or not. Of what clinical usefulness is the DST, since we must treat the patient and not the laboratory result? Many patients have normal results on the DST but are severely depressed, and vice versa; alcoholics and those taking psychotropic drugs, for example, will have positive DST results but not suffer from depression or require treatment (3).

Physicians from other countries are properly impressed with the glittering technology available to American physicians, but sometimes we would do better to use our eyes and ears and clinical judgment and do without costly and unnecessary workups. Clinical observation of depressed patients is not very difficult, after all. As for using the DST to determine whether the patient is recovering from depression or relapsing into it, any psychiatrist who needs a laboratory study to make that clinical determination needs more training in recognizing affective disorders. He or she also needs to quit using costly laboratory studies that drive up the cost of health care, especially when health care dollars are scarce.

Having written an article on the DST (4), I am in the curious position of being the only local psychiatrist who never uses it! Some psychiatrists have added the DST to their routine admission orders for all depressed patients, but how this affects the treatment the patients receive is obscure. Perhaps the guidelines for ordering the DST need clarification, but I think for now the DST is best left to researchers who can readily justify their use of it. I do not think clinicians need the test at all; it seems both unnecessary and costineffective.

#### REFERENCES

- Peselow ED, Baxter N, Fieve RR, et al: The dexamethasone suppression test as a monitor of clinical recovery. Am J Psychiatry 1987; 144:30–35
- Carroll BJ: The dexamethasone suppression test for melancholia. Br J Psychiatry 1982; 140:292–304
- Kraus RP, Hux M, Grof P: Psychotropic drug withdrawal and the dexamethasone suppression test. Am J Psychiatry 1987; 144: 82–85
- Solomon JG: Trait marker for mental illness: dexamethasone suppression test. Va Med 1983; 110:382–386

JONATHAN G. SOLOMON, M.D. Hampton, Va.

#### Dr. Peselow Replies

SIR: My colleagues and I appreciate Dr. Solomon's letter and are happy to hear that the results of our study concur with his clinical impression. We (and, I believe, most investigators) agree that the DST value should never replace clinical judgment in making decisions about treatment for depressed patients.

However, our impression regarding the DST is similar to that of the American Psychiatric Association's Task Force on Laboratory Tests in Psychiatry; i.e., we feel that although it may not be clinically helpful at this time, it would be premature to discard it entirely. It does seem clear that there is a greater frequency of abnormal DST results in patients with major depression, particularly the endogenous or melancholic subtype, than in other psychiatric groups (1). Although this difference is not as sensitive and specific as previously suggested (2), the difference does appear to suggest hypothalamic-pituitary-adrenal dysfunction, which may give us a clue to the etiology and treatment of depression.

Recent (3, 4) although disputed (5) evidence that positive results on the DST in depressed patients predict a poor response to placebo—suggesting the need for somatic treatment—might be important if replicated. In addition, despite our study, there is evidence in the literature (1) which contradicts our finding and suggests that the DST might be a useful predictor of clinical recovery. However, as Dr. Solomon correctly points out, one wonders how much this laboratory test adds to existing clinical judgment. In a study in which I was involved (4), the fact that the DST predicted poor response to placebo was not really useful clinically. The

mere fact that the patients presented with major depressive symptoms, which remained constant after a week of single-blind placebo, suggested the need for somatic treatment regardless of the DST results.

Thus, although my colleagues and I share Dr. Solomon's pessimism about the current clinical usefulness of the DST, we feel—on the basis of what I have just said—that further work is needed to truly elucidate its role in psychiatric treatment.

#### REFERENCES

- Arana GW, Baldessarini R, Ornsteen M: The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Arch Gen Psychiatry 1985; 42:1193–1204
- Carroll BJ, Feinberg M, Greden J, et al: A specific laboratory test for the diagnosis of melancholia—standardization, validation, and clinical utility. Arch Gen Psychiatry 1981; 38:292— 304
- 3. Shrivastava RK, Schwimmer R, Brown W, et al: DST predicts poor placebo response in depression, in New Research Abstracts, 138th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1985
- Peselow ED, Lautin A, Wolkin A, et al: The dexamethasone suppression test and response to placebo. J Clin Psychopharmacol 1986; 6:286–291
- Georgotas A, Stokes P, McCrue RE, et al: The usefulness of the DST in predicting response to antidepressants: a placebocontrolled study. J Affective Disord 1986; 11:21–28

ERIC D. PESELOW, M.D. Brooklyn, N.Y.

#### Posttraumatic Stress Disorder in Japanese Prisoners of War

SIR: The paper by Christopher C. Tennant, M.D., and associates on the psychological effects 40 years after release of being a prisoner of war (1) is misleading, particularly since posttraumatic stress disorder is less recognized in Australia than in the United States. The authors described posttraumatic stress disorder as "the presumed diagnosis," but in a later paper describing the same study (2), they went further and said, "No subjects . . . fulfilled the DSM-III requirements of post-traumatic stress disorder." The psychiatric methodology of the assessment is questionable. Together, the physical and psychological assessment of each subject took half a day, and there was no indication of the length of time given to the psychiatric interview. Furthermore, there was no confirmation of the validity of the psychodiagnostic instruments used in relation to posttraumatic stress disorder.

The Physician's Guide for Disability Evaluation and Examination (3) stresses that "interviews of cases for PTSD will often require more time than for other disorders." Furthermore, in the section Diagnostic Pitfalls, it states in relation to psychodiagnostic instruments, "As of the mid-1980s standardized instruments (e.g., the MMPI, DSI [sic], SCL-90 and SADS) have not been validated for PTSD and are not capable of sorting symptoms and responses into the diagnosis of PTSD. Until sufficient standardized research is complete, such instruments cannot be utilized to document the presence or absence of PTSD. They may even suggest alternative incorrect diagnoses."

McFarlane (4) stressed the frequency of multiple diagnoses on axis I in cases satisfying the criteria for a *DSM-III* diagnosis of posttraumatic stress disorder, and Green et al. (5), in a critical review of some of the conceptual issues involved with posttraumatic stress disorder, referred to

"shifts over time in symptom constellations or intensities" related to "fluctuations," "episodes," and "trigger stimuli." Shore et al. (6) indicated that their use of the Diagnostic Interview Schedule was the first application of a "new technique to a disaster community" and suggested that very careful use of this schedule is necessary to elicit "intensification" of symptoms provoked by situations that remind the individual of a traumatic experience, which, one might suppose, occur precisely when the "denial and suppression" referred to by Dr. Tennant and his colleagues is breached.

It cannot therefore be accepted that the study by Dr. Tennant and associates excluded the diagnosis of posttraumatic stress disorder in the postwar psychological morbidity of their subjects.

Green et al. (5) listed four possibilities for explaining the relationship between posttraumatic disorder and character pathology: 1) character pathology and posttraumatic stress disorder may be relatively independent, 2) character pathology may predispose individuals to develop posttraumatic stress disorder, 3) it may function as a selector for those who find themselves in high-risk, potentially traumatic situations and survive, and 4) character pathology may develop from trauma. A fifth possibility that they did not mention is that previous character (whether pathological or normal) may be one of the variables determining the final clinical picture in individuals with chronic posttraumatic stress disorder. With such a hypothesis it is quite possible that Dr. Tennant and associates were describing, among other things, the symptoms of chronic posttraumatic stress disorder sufferers, dependent as much on their premorbid personality as on any difference in the nature of the catastrophic stress they have experienced.

Finally, it should be pointed out that it would not be unreasonable to expect to find posttraumatic stress disorder in a number of the control subjects used in the study by Dr. Tennant and his colleagues.

#### REFERENCES

- Tennant CC, Goulston KJ, Dent OF: The psychological effects of being a prisoner of war: forty years after release. Am J Psychiatry 1986; 143:618-621
- Tennant C, Goulston K, Dent O: Australian prisoners of war of the Japanese: post-war hospitalisation and psychological morbidity. Aust NZ J Psychiatry 1986; 20:334–340
- The Physician's Guide for Disability Evaluation and Examination. Washington, DC, Veterans Administration, Department of Medicine and Surgery, 1985
- McFarlane A: Posttraumatic morbidity of a disaster: a study of cases presenting for psychiatric treatment. J Nerv Ment Dis 1986; 174:4–14
- Green BL, Lindy JD, Grace MC: Posttraumatic stress disorder: toward DSM-IV. J Nerv Ment Dis 1985; 173:406–411
- Shore JH, Tatum EL, Vollmer WM: Psychiatric reactions to disaster: the Mount St Helens experience. Am J Psychiatry 1986; 143:590-595

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### Dr. Tennant and Colleagues Reply

SIR: There is little disagreement between ourselves and Dr. Burges Watson. While we accept that the diagnosis of posttraumatic stress disorder is at times difficult, Dr. Tennant was experienced in this area, having worked full-time as a psychiatrist in a Veterans Hospital psychiatric department.

We had indeed expected to find subjects with posttraumatic stress disorder, but, using the strict DSM-III criteria, we could not identify any (1). Nonetheless, we believe that the excess morbidity we did find was clearly due to traumatic war stress. Irrespective of the mechanisms involved (in this case, the possibility that symptoms change over long periods of time or that these veterans had ego defenses which did not permit the expression of some clinical phenomena), a diagnosis according to DSM-III can only be based on observable or elicitable phenomena, not on phenomena that might be present in the unconscious.

We are not aware of any other published studies of survivors of catastrophic experiences of this magnitude, so long after the trauma, that have used standardized diagnostic (DSM) criteria. Comparison is thus not possible. It will be of great interest to see, in longitudinal studies of Vietnam veterans perhaps, whether posttraumatic stress disorder symptoms change over a 40-year period. It is our expectation that they will, and perhaps in the twenty-first century, although many will have considerable psychiatric morbidity, there will be few with DSM-III diagnoses of posttraumatic stress disorder.

# REFERENCE

 Tennant C, Goulston K, Dent O: Australian prisoners of war of the Japanese: post-war psychiatric hospitalisation and psychological morbidity. Aust NZ J Psychiatry 1986; 20:334

–340

> CHRISTOPHER TENNANT, M.D. KERRY GOULSTON, M.D. OWEN DENT, PH.D. St. Leonard's, N.S.W., Australia

# Use of Animals in Research

SIR: The "research perspective" set forth in the editorial by Harold Alan Pincus, M.D., and associates on the animal rights movement (1) appears to be that psychiatric research benefits human welfare; the use of animals, especially primates, benefits psychiatric research; and therefore, psychiatric researchers and clinicians should ensure that animal research continues as before.

We in the animal rights movement understand that the use of animals may aid psychiatric research. We also know that humans would provide a vastly superior psychiatric research model. Yet, as was correctly stated in the editorial, human subjects cannot be used for some studies. Understand that it is not for scientific reasons that humans cannot be used, but for ethical reasons. Understand also that it is not for scientific reasons alone that animals should not be used; there exist ethical reasons that pack their greatest punch when a nonhuman primate is the potential research subject.

The editorial simply assured us that researchers are "ethically concerned" about the use of animals, but nothing in the editorial showed that the authors understand what there is to be concerned about. Indeed, it is my experience that researchers generally have only a modest understanding of the difficult and powerful ethical issues that their animal research raises.

The same Congressional Office of Technology Assessment publication that was cited in the editorial (2) included a chapter which briefly reviewed the ethical considerations of animal experimentation. The chapter concluded that "animals are morally entitled to be treated humanely; whether they are entitled to more than that is unclear" (p. 83). The

failure of researchers to care enough to inform themselves deeply about these "unclear" ethical issues is moral blindness

The editorial states correctly that "the conduct of scientific inquiry is at stake" here. The duty of psychiatric researchers and clinicians, however, is not simply to ensure that animal research continues but to inform themselves about the ethical issues (the Congressional study is a good place to start), understand them, and enter the debate.

# REFERENCES

- Pincus HA, Fine T, Pardes H, et al: The animal rights movement: a research perspective (editorial). Am J Psychiatry 1986; 143: 1585-1586
- US Congress, Office of Technology Assessment: Alternatives to Animal Use in Research, Testing and Education. Washington, DC, US Government Printing Office, 1986

STEVEN M. WISE President, Animal Legal Defense Fund Boston, Mass.

# Dr. Pincus and Associates Reply

SIR: Mr. Wise's letter responding to our editorial about the appropriate role of animal models in the conduct of biomedical and behavioral research restates a position we articulated in our editorial: that animal research should continue if scientific knowledge and improved clinical interventions are to be advanced, and that researchers should continue to exercise care and discretion in the use of animal subjects. We stated unequivocally that "we must ensure against errors of judgment or protocol in animal research through better education of our researchers to the highest standards of animal care and concern."

Clearly, animal research does raise "difficult and powerful ethical issues." We have no reason to believe that psychiatric researchers have any greater or lesser understanding of these issues than do animal rights advocates. Mr. Wise's assertion that researchers are ignorant about ethics is simply an attempt to cloud what is, in fact, a fundamental, ethically based disagreement about the value of human life and welfare relative to that of the life and welfare of animals.

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# **Expressed Emotion**

SIR: Howard W. Koenigsberg, M.D., and Robert Handley, Ph.D. (1), took "expressed emotion" and tried to make it into an entity with their own definition. In general, I don't think it is a good idea to impose narrow technical definitions on the words of our common language, but I think they have a further problem by trying to make expressed emotion into an entity at all.

I think they know better; they have listened to families, and they wrote about the range of emotion families express. Throughout the paper, however, they hoped that if only they could draw the line in the right place, they could predict

which schizophrenic patients would "relapse" in which hostile families. Their failure is similar to the mess we have waded through with the dexamethasone suppression test; there is just no reason to think that a single variable will uniformly categorize human life events. In this case, I hope that the authors' index building does not distract from their promotion of focusing on how families express concern, exasperation, scorn, attachment, and so on.

# REFERENCE

Koenigsberg HW, Handley R: Expressed emotion: from predictive index to clinical construct. Am J Psychiatry 1986; 143: 1361-1373

MICHAEL STITELMAN, M.D. Branford, Conn.

# Drs. Koenigsberg and Handley Reply

SIR: Dr. Stitelman objects to the reductionistic use of a research variable to represent the complexity of family life. This is a principle worthy of support. However, while Dr. Stitelman takes exception to clinical reductionism, his reading of our paper as an exercise in "index building" is itself reductionistic.

The expressed emotion index was developed as part of an inductive process of research. Beginning with the observation by George Brown that schizophrenic patients who returned home following hospitalization were apt to relapse sooner than those who lived alone, researchers gradually identified a number of features of family attitude that correlated with early relapse. These features were codified into an expressed emotion index that was a strong and well-replicated predictor of relapse. The development of the index was not the end point, as Dr. Stitelman seems to believe, but, rather, a midway point in the inductive inquiry. Our review examined work seeking to dissect expressed emotion to identify clinically meaningful constructs underlying the index. Studies of family interaction patterns, relatives' personality styles, the effect of intercurrent life events, and psychophysiological responses of patients have helped elucidate the expressed emotion construct. Reviewing this work, we raised the possibility that expressed emotion may be an umbrella concept encompassing several core constructs, and we presented a number of alternative conceptualizations. The emphasis of our paper was on deriving clinically meaningful constructs from a predictive index, not on advocating its use simply to "draw the line," as Dr. Stitelman asserts.

He also makes the specific criticism that we claimed that a single variable, expressed emotion, predicts the course of schizophrenia. To the contrary, we discussed the role of a number of other predictor variables (p. 1363), and we displayed these variables in the fourth column of our table 1. It is only by unfolding the effect of other predictor variables that it becomes possible to assess the contribution of the expressed emotion variable itself.

We do agree with Dr. Stitelman's initial point: "expressed emotion" is a poor name for the construct. Unfortunately, the term has been widely used since its introduction in 1972, and it has become fairly well incorporated into our lexicon.

HAROLD W. KOENIGSBERG, M.D.

White Plains, N.Y.

ROBERT HANDLEY, PH.D.

Denver, Colo.

# Voluntary and Involuntary Patients

SIR: While sympathetic to the need to determine what differentiates "voluntary" psychiatry inpatients from those who are "involuntary" in order to better decide loci of treatment, we take issue with the approach of Robert L. Okin, M.D., in his article on legal status and characteristics of patients in state hospitals (1).

In the article the only reason for not equating voluntariness with legal status was that "some patients who sign into state hospitals voluntarily may in fact do so under the threat that they would otherwise be admitted involuntarily." There are others. In Massachusetts, where the state hospitals are the first line of treatment and not backup facilities, patients are transported from outpatient settings directly to hospitals. Police departments and ambulances will not transport patients without a physician's emergency certification. Hence, patients who would otherwise be voluntary arrive at the hospital as involuntary patients. Sometimes they sign in voluntarily, and sometimes they do not. Furthermore, involuntary patients who know the system well often sign in voluntarily. By doing so they can simultaneously execute a 3-day notice, in an attempt to be discharged sooner than if they had remained involuntary patients. In Massachusetts, legal status on admission has little relationship to patients' willingness to be at the facility.

The confusion surrounding voluntariness is compounded by the questionable competency of many individuals who sign voluntary admission forms. Olin and Olin (2), in a study done in Massachusetts, found that only 8% of those who signed into a state hospital voluntarily had a full understanding of the voluntary admission contract. Studies in other states have had similar outcomes (3, 4).

State hospitals—unlike general hospitals and private psychiatric hospitals—serve a population skewed toward chronicity of illness, previous utilization of services, familiarity with the inpatient setting, and lack of third-party reimbursement. How these make an impact on legal status at the time of admission is important and may override the effects of current clinical status. It is not clear that those who are now voluntary and involuntary patients at a state hospital are the same as those who would become voluntary and involuntary patients at a general hospital psychiatric unit.

Understanding the operation of the Massachusetts system makes some of Dr. Okin's "unanticipated" findings less surprising. One example: involuntary patients were found to have fewer previous psychiatric admissions and shorter lengths of stay than voluntary patients. It is common for an individual—without the knowledge of the community mental health system—to be involuntarily admitted to a Massachusetts state hospital and then promptly transferred to the private sector when insurance coverage is verified and/or a bed is available.

Dr. Okin, while Commissioner of Mental Health in Massachusetts, was a strong advocate for general hospital psychiatric units to replace some functions historically fulfilled by state hospitals. We supported that concept then and continue to do so. Unfortunately, Dr. Okin's article does not assist us in evaluating the viability of that option. Legal status at admission and voluntariness—in Massachusetts, at least—are far from synonymous.

# REFERENCES

 Okin RL: The relationship between legal status and patient characteristics in state hospitals. Am J Psychiatry 1986; 143: 1233–1237

- Olin GB, Olin HS: Informed consent in voluntary mental hospital admissions. Am J Psychiatry 1975; 132:938–941
- Palmer AB, Wohl J: Voluntary-admission forms: does the patient know what he's signing? Hosp Community Psychiatry 1972; 23: 250–252
- Berg A, Hammitt KB: Assessing the psychiatric patient's ability to meet the literacy demands of hospitalization. Hosp Community Psychiatry 1980; 31:266–268

JEFFREY L. GELLER, M.D., M.P.H. STEVEN K. HOGE, M.D. Worcester, Mass.

# Dr. Okin Replies

SIR: Drs. Geller and Hoge assert that I equated legal status with voluntariness. I did not. In fact, I explicitly stated that certain factors erode and blur the real distinction between voluntary and involuntary patients. I gave one important example of such a factor. There are obviously others, as Drs. Geller and Hoge have pointed out.

Drs. Geller and Hoge also imply that my study would have been better designed had it examined the correlation between de facto voluntariness (rather than formal legal status) and other characteristics of patients. The two reasons that formal legal status was chosen instead were 1) the difficulty of assessing de facto voluntariness, which involves a great degree of subjectivity on the part of the researcher, and 2) the fact that one of the major exclusion criteria of many general hospitals involves formal legal status, not simply de facto voluntariness. The entire point of the paper, in fact, was to demonstrate that formal legal status does not necessarily imply much about the clinical status of the patient and thus should not by itself be used as an exclusion criterion in the general hospital admission process.

ROBERT L. OKIN, M.D. Boston, Mass.

# Differential Diagnosis of Mute Patients

SIR: I was pleased to read the helpful and sensible review of mutism by Lori L. Altshuler, M.D., and associates (1). However, while stressing the importance of diagnosing organic disease that presents in this way, they unfortunately repeated the erroneous assumption—made by many eminent physicians since Charcot—that a mute patient's ability to whisper and write intelligibly confirms the diagnosis of hysterical conversion or some other psychiatric condition. I reported just such a case (2); the patient was found to have a left frontoparietal infarction and probably had a highly specific apraxia of speech.

Furthermore, the authors glossed over the distinction between near speechlessness and total speechlessness. It is the latter that, in the absence of any other physical signs, is most likely to be "functional" in origin (3). However, in this area, as in the whole of medicine, there are exceptions to every rule.

# REFERENCES

- Altshuler LL, Cummings JL, Mills MJ: Mutism: review, differential diagnosis, and report of 22 cases. Am J Psychiatry 1986; 143:1409–1414
- David AS, Bone I: Mutism following left hemisphere infarction.
   J Neurol Neurosurg Psychiatry 1984; 47:1342–1344

3. Critchley M: Total speechlessness, in Aphasiology. London, Edward Arnold, 1970

ANTHONY S. DAVID, M.R.C.P. London, England

# Dr. Altshuler and Associates Reply

SIR: We would like to thank Dr. David for refocusing attention on two important aspects of the diagnosis of mute patients: 1) the need to determine whether the patient can write and 2) the distinction between near and total speechlessness. Mutism with a concomitant preservation of the ability to write may occur in some psychiatric disorders 'e.g., conversion reactions with aphonia, depression, catatonic schizophrenia) but may also occur, as Dr. David states, in neurologic conditions. Aphemia, the syndrome mentioned by Dr. David, is characterized by mutism, transient right hemiparesis, and retained ability to write (1). It usually occurs with a small lesion in Broca's area of the left hemisphere. We alluded to this disorder in our review of mutism and included it in the list of differential diagnoses at the end of the article.

The distinction between near and total speechlessness requires further study. There are at least three syndromes in which speech is reduced but the patient is not completely mute. In the first, the patient has no verbal output for long periods but occasionally interrupts his or her silence with statements of normal volume and structure. This may occur in catatonic states of neurologic or psychiatric origin and in akinetic mutism. The second syndrome includes all of the nonfluent aphasias, such as transcortical motor aphasia, Broca's aphasia, and global aphasia. These patients have a paucity of verbal output but can execute brief expostulations and single-word replies. The third syndrome includes patients whose speech is markedly diminished in volume, so that whispering is the predominant mode of communication. This behavior may occur with conversion disorders and depression but may also be seen with vocal cord lesions and in the recovery phases of aphemia.

We agree with Dr. David that there are exceptions to virtually all rules regarding the mute patient, and there is no substitute for a thorough evaluation guided by knowledge of the differential diagnosis and continued observation until a diagnosis can be confirmed. Only then will the silent patient begin to yield his or her secrets.

# REFERENCE

 Benson DF: Aphasia, Alexia, and Agraphia. New York, Churchill Livingstone, 1979

> LORI L. ALTSHULER, M.D. JEFFREY L. CUMMINGS, M.D. MARK J. MILLS, J.D., M.D. Los Angeles. Calif.

# Torture and the Legal System

SIR: In her review of *The Breaking of Bodies and Minds: Torture, Psychiatric Abuse, and the Health Professions* (1), Lisa M. Schwerdt, Ph.D., wrote that torture was not cast from the legal system until Napoleon did so in 1808. This is historically not quite correct. The first governing head of state who officially struck torture from the legal system of his

country was Frederick II (the Great), when he became king of Prussia in 1740.

REFERENCE

 Schwerdt LM: Book review, E Stover, EO Nightingale (eds): The Breaking of Bodies and Minds: Torture, Psychiatric Abuse, and the Health Professions. Am J Psychiatry 1987; 144:115–116

HEINRICH FUERST, M.D. Nanoose Bay, B.C., Canada

# Dr. Schwerdt Replies

SIR: My statement was based on information contained in Stover and Nightingale's book. I appreciate Dr. Fuerst's

correction of the facts, which emphasizes even more the need for attention to this matter.

LISA M. SCHWERDT, PH.D. Florence, Ala.

# Correction

In the article "Psychiatric Disorders in a Community Sample of Adolescents" (May 1987 issue, pp. 584–589) by Javad H. Kashani, M.D., et al., there was an error in the fourth paragraph on page 585. The number 115 (72.4%) should have been 155 (72.4%).

The staff regrets the error.

Reprints of letters to the Editor are not available.

# Highlights of the 140th Annual Meeting

The 140th annual meeting of the American Psychiatric Association was held in Chicago, Ill., May 9–14, 1987. The total registration was 11,312, including 6,134 members, 1,396 spouses and other family members, 1,870 nonmember professionals, 1,433 exhibitors, 186 members of the media, and 137 staff members.

# Opening Session

The opening session was called to order by Robert O. Pasnau, M.D., 115th President of the Association, on Sunday evening, May 10, in the Arie Crown Theatre, McCormick Place East. Dr. Pasnau read a letter of welcome from Mayor Harold W. Washington.

Dr. Pasnau recognized members of the APA board of Trustees, members of the Executive Committee of the APA Assembly, past Presidents, past Speakers of the Assembly, past Vice-Presidents of the Association, and newly elected national and Assembly officers, Trustees, presidents of APA district branches, and chairpersons of the APA councils.

Dr. Pasnau announced that Dr. Anatoly Koryagin, who had recently been released from prison in the Soviet Union and emigrated to Switzerland, would hold a press conference and give a talk to the Association on Wednesday, May 13.

Robert E. Hales, M.D., chairperson of the Scientific Program Committee, and Harold M. Visotsky, M.D., and James T. Barter, M.D., co-chairpersons of the Local Arrangements Committee, were introduced and thanked by Dr. Pasnau.

Dr. Pasnau then introduced the following distinguished representatives of psychiatric and other related organizations from the United States and abroad:

International scholars: Prof. Costas Stefanis of Greece, also representing the World Psychiatric Association; Prof. Andrzej Piotrowski of Poland, also representing the Polish Psychiatric Association; Prof. Brij B. Sethi of India, also representing the Indian Psychiatric Society; Prof. Hanns Hippius of West Germany; and Dr. David Hamburg of the United States.

Representatives of other international organizations and psychiatric associations in other countries: Dr. Anne Lindhardt, Danish Psychiatric Society; Prof. Dr. E. Lungershausen, German Society for Psychiatry and Neurology; Dr. Rodolfo Fahrer, Argentinian Association for Social Psychiatry; Dr. Ho Young Lee, Korean Neuropsychiatric Association; Prof. A. Ledesma Jimeno, Spanish Society of Psychiatrists; Dr. Paulo Alterwain, Ministry of Health of Uruguay; Prof. F. Lieh Mak, Hong Kong Psychiatric Association; Dr. Masahisa Nishizono, Japanese Psychoanalytic Association; Prof. Eng-Kung Yeh, Taiwan Society of Psychiatry and Neurology; Dr. Kyoshi Makita, Pacific Rim College of Psychiatrists; Prof. Jorge Alberto Costa e Silva, Brazilian Association for Social Psychiatry; Dr. John Grigor, Royal Australian and New Zealand College of Psychiatrists; Dr. Satoshi Shikiba, Japanese Society for Private Psychiatric Hospitals; Dr. J.L.T. Birley, Royal College of Psychiatrists of Great Britain; Prof. Dr. W.J. Schudel, Dutch Psychiatric Association; Dr. Stanley Greben, Canadian Psychiatric Association; Dr. Hannes Petursson, Icelandic Psychiatric Association; Dr. Nalaka Mendis, Sri Lanka Psychiatric Society; Dr. Manoel Antonio Albuquerque, Latin American Psychiatric Association; Dr. John Carleton, World Association for Social Psychiatry; Dr. Douglas Matamoros, Neurological Society of Honduras; Dr. Roberto Llanos Zuloaga, Peruvian Psychiatric Association; Dr. Kari Pylkkanen, Finnish Psychiatric Association; Dr. Fathy Loza, Egyptian Psychiatric Association; Dr. Otto Doerr, Chilean Society of Neurology, Psychiatry, and Neurosciences; Dr. Elena Levin, Argentine Psychiatric Association; Dr. Constantine Soldatas, Hellenic Society of Neurology and Psychiatry; Dr. Nicholas Destounis, Hellenic Society of Psychosomatic Medicine of Greece and the American Branch of the World Association of Dynamic Psychiatry; and Dr. Abraham Halpern, International Society of Law and Psychiatry.

Representatives of organizations in the United States: Dr. William L. Webb, Jr., President, Academy of Psychosomatic Medicine; Dr. Donald Ian Macdonald, Administrator, Alcohol, Drug Abuse, and Mental Health Administration; Dr. Irving Philips, President, American Academy of Child and Adolescent Psychiatry; Dr. Rodrigo A. Muñoz, President, American Academy of Clinical Psychiatrists; Dr. Jack D. Kerth, representing the American Academy of Otolaryngology-Head and Neck Surgery; Dr. Richard J. Frances, President, American Academy of Psychiatrists in Alcoholism and Addictions; Dr. J. Richard Ciccone, President, American Academy of Psychiatry and the Law; Dr. Arthur W. Epstein, President, American Academy of Psychoanalysis; Dr. Elliott M. Stein, President, American Association for Geriatric Psychiatry; Dr. Gene L. Usdin, President, American Association for Social Psychiatry; Dr. Herbert Pardes, President, American Association of Chairmen of Departments of Psychiatry; Dr. Gordon H. Clark, President, American Association of Community Mental Health Center Psychiatrists; Dr. George L. Ginsberg, President, American Association of Directors of Psychiatric Residency Training, Inc.; Dr. Stuart L. Keill, President, American Association of General Hospital Psychiatrists; Dr. Dave M. Davis, President, American Association of Psychiatric Administrators; Dr. Girish V. Shah, President, American Association of Psychiatrists From India; Dr. Joseph D. Bloom, President, American Board of Forensic Psychiatry, Inc.; Dr. John A. Talbott, Vice-President, American Board of Psychiatry and Neurology, Inc.; Dr. Robert L. Leon, President, American College of Psychiatrists; Dr. Alex H. Kaplan, President, American College of Psychoanalysts; Dr. Howard D. Kibel, President, American Group Psychotherapy Association; Dr. John L. Clowe, Vice-Speaker, House of Delegates, American Medical Association; Dr. Mary Jane England, President, American Medical Women's Association; Dr. Barry Aranson, representing the American Neurological Association; Ms. Kathleen Scharer, representing the American Nurses Association; Dr. Bert Pepper, President, American Orthopsychiatric Association; Mrs. Judith Feldman, President, American Psychiatric Association Auxiliary; Dr. Richard C. Simons, President, American Psychoanalytic Association; Dr. Bonnie R. Strickland, President, American Psychological Association; Dr. Lee N. Robins, President, American Psychopathological Association; Dr. John G. Looney, President, American Society for Adolescent Psychiatry; Dr. Evaristo Gomez, President, American Society of Hispanic Psychiatrists; Dr. Paul S. Appelbaum, representing the American Society of Law and Medicine; Dr. Milton

Reisner, President, American Society of Psychoanalytic Physicians; Dr. Nabil El-Rafei, President, Arabic-Speaking Psychiatrists of America; Dr. Jonathan F. Borus, President, Association for Academic Psychiatry; Dr. John N. Chappel, President, Association for Medical Education and Research in Substance Abuse; Dr. Chase P. Kimball, President, Association of Directors of Medical Student Education in Psychiatry; Father Lucien Sawyer, President, Association of Mental Health Clergy; Dr. Robert L. Williams, President, Benjamin Rush Society; Dr. Richard A. Fields, President, Black Psychiatrists of America; Dr. Jerry M. Lewis, President, Group for the Advancement of Psychiatry; Dr. Ewald W. Busse, President, International Association of Gerontology; Mr. Donald J. Richardson, President, National Alliance for the Mentally Ill; Mr. Malcolm D. Strickler, President, National Association of Private Psychiatric Hospitals; Ms. Dorothy V. Harris, President, National Association of Social Workers; Dr. J. Frank James, President, National Association of State Mental Health Program Directors; Ms. Marilyn Weiss, President, National Depressive and Manic-Depressive Association; Dr. Thomas K. Ciesla, President, National Guild of Catholic Psychiatrists; Dr. Dorynne Czechowicz, Assistant Director for Medical and Professional Affairs, National Institute on Drug Abuse; Dr. Frank J. Sullivan, Acting Director, National Institute of Mental Health; Mrs. Suzanne G. Elson, President, National Mental Health Association; Dr. Syed Arshad Husain, President, Pakistan Psychiatric Society of America; Dr. Mario A. Ordonez, President, Philippine Psychiatrists in America; Dr. Everett H. Ellinwood, President, Society of Biological Psychiatry; Dr. Norbert Enzer, President-Elect, Society of Professors of Child Psychiatry; and Dr. M. Kemal Goknar, President, Turkish-American Neuropsychiatric Associa-

George Tarjan, M.D., introduced Dr. Pasnau, who gave the Presidential Address, "Psychiatry in Medicine: Medicine in Psychiatry" (printed elsewhere in this issue of the *Journal*). Harold M. Visotsky, M.D., introduced George H. Pollock, M.D., President-Elect of the Association, who gave the Response to the Presidential Address, "Opportunities and Challenges That Confront Medicine and Its Specialties, With Special Reference to Psychiatry (printed elsewhere in this issue). Dr. Pasnau then adjourned the opening session.

# Business Meeting

The annual business meeting was called to order by Robert O. Pasnau, M.D., in McCormick Place North on Monday, May 11, 1987, at 12:30 p.m.

First session. Dr. Pasnau asked for a moment of silence in memory of all members and Fellows who had died during the past year. John S. McIntyre, M.D., Recorder, called the roll of Assembly representatives and announced the presence of a quorum. Edward C. Kirby, M.D., chairperson of the Tellers Committee, announced the results of the election of officers and Trustees.

The reports to the membership followed. Each officer submitted a report to the Assembly, acting for the membership, and gave a brief summary of that report. Elissa P. Benedek, M.D., presented the Secretary's report, which was followed by the reports of Alan I. Levenson, M.D., Treasurer; Roger Peele, M.D., Speaker of the Assembly; Irvin M. Cohen, M.D., Speaker-Elect of the Assembly; Leigh M. Roberts, M.D., chairperson of the Committee on Constitution and By-Laws; and John S. McIntyre, M.D., chairperson of the Membership Committee. Melvin Sabshin, M.D., presented the Medical Director's report. Reports of all the councils were also available. All reports were accepted by the Assembly as submitted and will be published in the October 1987 issue of the American Journal of Psychiatry.

Dr. Pasnau presented the Speaker's plaque to Roger Peele, M.D., retiring Speaker, and the Vice-President's badge to Paul J. Fink, M.D., retiring Vice-President. Daniel X. Freedman, M.D., presented the President's badge to Dr. Pasnau. Dr. Pasnau then recessed the first session of the business meeting.

Second session. Dr. Pasnau called the second session of the business meeting to order and opened the forum. There were no requests from the floor for discussion of new business. The business meeting was then adjourned by Dr. Pasnau.

# Convocation

The 31st Convocation of Fellows was held in the International Ballroom of the Chicago Hilton Hotel, beginning at 8:00 p.m. on Monday, May 11. Dr. Pasnau presided. After the processional march, Dr. Pasnau called the convocation to order. The invocation was given by the Reverend Edwin Wappler, Ph.D., of Grace Episcopal Church, Oak Park, Ill. President-Elect Pollock then led the ceremony conferring Life Fellowship and the induction of Fellows of the Association. Dr. Pasnau introduced Distinguished Fellow Floyd E. Bloom, M.D., and Honorary Fellow Janet B.W. Williams, D.S.W., and read the names of the 1986 Corresponding Fellows, who were not present: M. Parameshvara Deva, M.D., Selangor, Malaysia; Franco Ferracuti, M.D., Rome, Italy; and Beverley Raphael, M.D., New South Wales, Australia. The following Life Fellows and Life Members who have been members of the Association for 50 years (1937–1987) were introduced:

Camilla M. Anderson, M.D., Sidney, Mont.; Irma Bache, M.D., Washington, D.C.; Thomas Bamford, Jr., M.D., San Diego, Calif.; Murray Bergman, M.D., Newark, N.Y.; Samuel B. Broder, M.D., Chicago, Ill.; Morris W. Brody, M.D., Bala-Cynwyd, Pa.; Edward J. Carroll, M.D., Miami, Fla.; James M. Cunningham, M.D., Dayton, Ohio; Raymond J. Duffy, M.D., Pacific Palisades, Calif.; Eugene Falstein, M.D., Chicago, Ill.; Michael Greenfield, M.D., Danville, Ill.; Roy R. Grinker, Sr., M.D., Chicago, Ill.; Harold B. Hanson, M.D., Edina, Minn.; Thomas J. Hardgrove, M.D., Sacramento, Calif.; James M. Henninger, M.D., Green Valley, Ariz.; Edward J. Humphreys, M.D., Hopewell, N.J.; Robert C. Hunt, M.D., Miami, Fla.; William K. Keller, M.D., Louisville, Ky.; Jules H. Masserman, M.D., Chicago, Ill.; Genevieve M.S. May, M.D., Malibu, Calif.; John D. Morgan, M.D., Portland, Ore.; Richard Newman, M.D., Woodbridge, Conn.; Mollie E. Orloff, M.D., Atlanta, Ga.; Tracy C. Owens, M.D., Indianapolis, Ind.; George E. Peatrick, Wayne, N.J.; Norman Reider, M.D., San Francisco, Calif.; Wendell H. Rooks, M.D., Grand Rapids, Mich.; J.L. Rosenbloom, M.D., Pueblo, Colo.; Joseph S. Skobba, M.D., Atlanta, Ga.; Stanislaus A. Szurek, M.D., Hillsborough, Calif.; Charles V. Taylor, M.D., Little Rock, Ark.; Mary M. Thomson, M.D., New York, N.Y.; Anthony S. Tornay, M.D., Philadelphia, Pa.; Carl E. Trapp, M.D., Glendale, Ariz.; Max Unger, M.D., Los Angeles, Calif.; Morton L. Wadsworth, M.D., Richmond, Va.; Raymond W. Waggoner, Sr., M.D., Ann Arbor, Mich.; Samuel R. Warson, M.D., Sarasota, Fla.; Paul L. White, M.D., Austin, Tex.; Leston S. Whitehead, M.D., Grosse Pointe, Mich.; Samuel A. Zeritsky, M.D., Philadelphia, Pa.; Max Zuger, M.D., Sarasota, Fla.

After introducing several members of the Menninger family who were in the audience, Dr. Pasnau introduced James H. Sammons, M.D., Executive Vice-President of the American Medical Association, who gave the William C. Menninger Memorial Convocation Lecture, "Where Has Adolescence Gone?"

Dr. Pasnau introduced the chairpersons of the awards committees and then presented the 1987 awards. Special Presidential Commendations were presented to Thomas F. Anders; M.D., Associate Chairman of the Department of Psychiatry and Human Behavior and Director of the Division of Child and Adolescent Psychiatry, Brown University, "in appreciation of his dedication and his many contributions to clinical practice and research, bridging the gap between pediatrics and child psychiatry"; to Norman Q. Brill, M.D., former Medical Director of UCLA's Neuropsychiatric Institute, "in appreciation of his dedication and his lifetime of teaching and clinical research in electroencephalography, neurology, psychiatry, and psychoanalysis, and his longstanding advocacy of psychiatry as a medical specialty"; to James S. Eaton, Jr., M.D., Clinical Professor of Psychiatry, Georgetown University Medical School, "in appreciation of his dedication and his continued support of curriculum development in psychiatry in medicine during his many years as chief of the Psychiatric Education Branch, NIMH"; to Zbigniew J. Lipowski, M.D., Professor of Psychiatry, University of Toronto Clarke Institute of Psychiatry, "in appreciation of his dedication and his lifetime of teaching and leadership in the development of the subspecialty of consultation-liaison psychiatry, and for his pioneering work in the delivery of psychiatric care to the physically ill"; to Carolyn B. Robinowitz, M.D., Deputy Medical Director of APA, "in appreciation of her dedication and her extraordinary leadership of medical organizations, including her presidencies of the ABPN and the CMSS, as well as her advocacy of psychiatry in medicine and pediatrics in her role as the director of the APA Office of Education"; to Robert L. Spitzer, M.D., Chief of Psychiatric Research, Biometrics Research Department, New York State Psychiatric Institute, "in appreciation of his dedication to the remedicalization of psychiatry through his significant contributions to an empirically based psychiatric nosology"; and to Herbert M. Weiner, M.D., Professor, Department of Psychiatry and Behavioral Sciences, UCLA, "in appreciation of his dedication and his outstanding research, scholarship, and teaching in psychosomatic and psychophysiologic interactions, and the maintenance of the highest scientific standards during his years as editor of Psychosomatic Medicine."

Distinguished Service Awards were presented by Dr. Pasnau to Henry W. Brosin, M.D., a former President of APA; to Robert J. Campbell, III, M.D., Director and Chief Executive Officer of Gracie Square Hospital in New York City and Editor-in-Chief of Psychiatric News; and to the American Association of Directors of Psychiatric Residency Training, whose award was accepted by its president, William Sledge, M.D. The award was established by the Trustees to honor members "whose distinguished careers have

ennobled the profession of psychiatry.'

Miles F. Shore, M.D., Bullard Professor of Psychiatry at Harvard Medical School and Superintendent of the Massachusetts Mental Health Center, received the Administrative Psychiatry Award. This award is given to an APA member who has served as a clinician executive in administration, excelled in the administration of major mental health programs, and served as a role model.

The APA/Pennwalt Resident Research Award, given for excellence in research undertaken during residency, was given to Daniel C. Javitt, M.D., a resident in psychiatry at Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, N.Y., and to Robert C. Malenka, M.D., a resident in psychiatry at Stanford University

School of Medicine.

The Marie H. Eldredge Award was given to Daniel G. Amen, M.D., Child Psychiatry Fellow at Tripler Army Medical Center in Hawaii. The award is given to an APA member or resident residing in Hawaii, Pennsylvania, or New Jersey to recognize research into the causes and treatment of neuroses and retardation.

Nancy C. Andreasen, M.D., Professor of Psychiatry at the University of Iowa College of Medicine, received the Foundations' Fund Prize for Research in Psychiatry. The prize honors those who have made distinguished contributions to research in psychiatry.

The Samuel G. Hibbs Award was presented to Lenore C. Terr, M.D., Clinical Professor of Psychiatry at the University of California, San Francisco. The award is given for the best unpublished paper on a clinical subject.

The Agnes Purcell McGavin Award, given to honor those who have made outstanding contributions to the prevention of mental disorders in children, was presented to Barbara Fish, M.D., Profes-

sor of Psychiatry at the UCLA School of Medicine.

Four writers received the Robert T. Morse Writers Award, given to honor popular writers who have made major contributions to public understanding of psychiatry over an extended period of time: Philip M. Boffey, Erik Eckholm, Daniel Goleman, and Harold M. Schmeck, Jr., all of the New York Times.

Robert Jay Lifton, M.D., Distinguished Professor of Psychiatry and Psychology at the City University of New York, received the Oskar Pfister Award, which honors outstanding contributions to issues of mutual interest to religious leaders and psychiatrists.

The Psychiatric Institutes of America Foundation Hospital Psychiatry Research Award, given in recognition of outstanding contributions in hospital psychiatry research as evidenced by research papers in the field of hospital psychiatry, was presented to three individuals: Jeffrey A. Borenstein, M.D., a resident in psychiatry at New York University Medical Center; Ira D. Glick, M.D., Professor of Psychiatry at Cornell University Medical College; and Jon E. Gudeman, M.D., Associate Professor of Psychiatry at the Harvard Medical School and Director of the Massachusetts Mental Health Center.

The Robert L. Robinson Award was given to Eileen Brennan, community outreach director for Channel 8, KFMB-TV, in San Diego; and to Michelle Trudeau, producer of a series on severe mental illnesses for National Public Radio. The award recognizes outstanding broadcasters whose work has significantly contributed to public understanding of psychiatry and mental illness.

The Arnold L. van Ameringen Award in Psychiatric Rehabilitation was presented to the Mental Health Law Project, a nonprofit public interest organization working to bring mentally disabled people under the full protection of the nation's laws and to generate adequate services to meet their needs. The award was accepted by Norman S. Rosenberg, director of the project. It honors contributions in one or more of the areas of service, research, education, and advocacy in the field of psychiatric rehabilitation and the care of the chronically mentally ill.

Louis Jolyon West, M.D., Professor and Chairman of the Department of Psychiatry and Biobehavioral Sciences at the UCLA School of Medicine, received the Seymour D. Vestermark Award, given for outstanding contributions to undergraduate and postgraduate medical education, continuing education, and education of behavioral

scientists for research in psychiatry.

The Jack Weinberg Memorial Award for Geriatric Psychiatry was presented to Martin A. Berezin, M.D., Clinical Professor Emeritus at Harvard Medical School. The award honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research in geriatric psychiatry

After the presentation of these awards, Dr. Pasnau adjourned the

Convocation.

Awards presented at meetings other than the Convocation in-

cluded the following:

The Manfred S. Guttmacher Award, given to honor outstanding contributions to the literature of forensic psychiatry, was given to attorney Jan Brakel, a staff researcher with the American Bar Foundation; John W. Parry, Director of the American Bar Association Commission on the Mentally Disbled; and Barbara A. Weiner, Assistant Professor of Clinical Psychiatry and Behavioral Sciences at Northwestern University Medical School and an adjunct professor at Chicago Kent College of Law.

The Adolf Meyer Award was presented to Robert L. Spitzer, M.D., chairperson of APA's Work Group to Revise DSM-111.

The Benjamin Rush Award was presented to Ilza Veith, M.D., Professor of Psychiatry at the University of California, San

Carlos A. León, M.D., Professor of Psychiatry at the medical school of the Universidad del Valle, Cali, Colombia, was the recipient of the Simon Bolivar Award.

The Solomon Carter Fuller Award was presented to Lerone Bennett, Jr., a senior editor at Ebony magazine.

The District Branch Newsletter of the Year Awards were given to the Florida Psychiatric Society Newsletter, Richard E. Gordon, M.D., Editor; and the PMA Newsletter of the Psychiatric Medical Association of New Mexico, Jay Feierman, M.D., Editor.

Scientific Sessions

The Scientific Program began on Monday, May 11, but Continuing Medical Education (CME) courses and industry-sponsored symposia began on Saturday, May 9. There were 27 discussion groups, 110 symposia (including 14 industry-sponsored symposia), 245 new research presentations, three scientific debates, papers presented in 50 paper sessions, 96 workshops (including 37 APA component presentations), 15 films, 37 videotapes, 85 CME courses, four medical updates, six annual reviews, three clinical case conferences, one continuous case conference, eight "clinical consultations with," and a public symposium.

There were 25 lectures. The speakers, their current positions, and

the titles of their presentations are listed here.

On Monday, May 11, the following speakers gave lectures: Jonathan F. Borus, M.D., Director of Residency Training at Massachusetts General Hospital and Associate Professor of Psychiatry at Harvard Medical School, "Academic Psychiatry: Teachers. Students, Colleagues"; Torsten Wiesel, M.D., Nobel laureate and head of a laboratory in neurobiology at Rockefeller University, "The Role of Experience in Shaping Cortical Circuitry"; Ethel S. Person, M.D., Director of the Columbia University Center for Psychoanalytic Training and Research, "Love Throughout the Life Cycle: Health and Disease"; Louis Jolyon West, M.D., Professor and Chairman of the Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, the Seymour D. Vestermark Lecture, "Terrorism, Torture, and the American Psychiatrist"; Lenore C. Terr, M.D., Clinical Professor of Psychiatry, University of California, San Francisco, the Samuel G. Hibbs Lecture, "The Trauma-Stress Disorders: An Outline and Overview"; Dennis S. O'Leary, M.D., President of the Joint Commission on the Accreditation of Hospitals, "Future Trends in Evaluating Quality of Care"; and Hanns Hippius, M.D., Chairman of the Department of Psychiatry, the University of Munich, "What Has Happened in Psychiatry Between Emil Kraepelin and the DSM-III?"

On Tuesday, May 12, the following lectures were given: Nancy C. Andreasen, M.D., Professor of Psychiatry at the University of Iowa, "Through a Skull Darkly: Seeing the Brain"; Costas N. Stefanis, M.D., Professor and Chairman of the Department of Psychiatry, Athens University Medical School, "Tomorrow's Psychiatrist: An International Perspective"; Allan Beigel, M.D., Professor of Psychiatry, the University of Arizona, "Avoiding the Potholes on the Road From Bedlam to Biotechnology"; Miles F. Shore, M.D., Bullard Professor of Psychiatry at Harvard Medical School, the Administrative Psychiatry Lecture, "Administration and the Third Ear"; Ilza Veith, M.D., Professor of Psychiatry, the University of California, San Francisco, the Benjamin Rush Lecture, "Benjamin Rush: Psychiatrist, Physician, and Social Reformer"; Lerone Bennett, Jr., Senior Editor, Ebony magazine, the Solomon Carter Fuller Lecture, "The Challenge of Blackness"; and Brij Bhushan Sethi, D.Sc., head of the World Health Organization Centre for Research and Training in Mental Health, "Emerging Trends in Mental Health in Developing Countries (India)."

On Wednesday, May 13, the following lectures were presented: Henry H. Work, M.D., Professor Emeritus of Psychiatry at the UCLA School of Medicine, "The Menace of Psychiatry: II"; Andrzej Piotrowski, M.D., President of the Polish Psychiatric Association, "Drug Abuse in Poland: Similarities and Dissimilarities with the World Scene"; Robert L. Spitzer, M.D., Chairperson of the APA Work Group to Revise DSM-III, The Adolf Meyer Lecture, "A Critical Look at Psychiatric Diagnosis: Where Are We and Where Should We Go?"; Carlos A. León, M.D., Professor of Psychiatry at the medical school of the Universidad del Valle, Cali, Colombia, the Simon Bolivar Lecture, "Observing Violence: A Latin American View"; David A. Hamburg, M.D., President of the Carnegie Corporation of New York, "Health and Behavior: A Worldwide Opportunity"; and Robert Jay Lifton, M.D., Distinguished Professor of Psychiatry and Psychology at the City University of New York, the Oskar Pfister Lecture, "The Psychological Uncovering of Evil: Nazi Doctors, 'Doubling,' and Genocide."

The lectures presented on Thursday, May 14, were the following: George D. Lundberg, M.D., Editor of the Journal of the American Medical Association, "Psychiatry and Medicine: How Do They Mix?"; T. Berry Brazelton, M.D., Chief of the Division of Child Development, Children's Hospital, Boston, "Importance of Early Intervention"; Sherry Turkle, Ph.D., Associate Professor of Sociology, Massachusetts Institute of Technology, "Computers and Psychological Development"; and Marian Wright Edelman, LL.B., founder and President of the Children's Defense Fund, "Children at Risk."

# Special Address by Dr. Anatoly Koryagin

Dr. Anatoly Koryagin, a Russian psychiatrist and member of APA, who was imprisoned for 6 years for his outspoken stance against the use of psychiatry for political purposes in the Soviet Union, was recently released from a labor camp and emigrated to Switzerland. Dr. Koryagin held a press conference and then addressed the members of APA on Wednesday, May 13, speaking of his experiences as a psychiatrist and as a political prisoner.

# Other Activities

The Committee on Local Arrangements, Harold M. Visotsky, M.D., and James T. Barter, M.D., co-chairpersons, planned many activities. A "fun run" and tennis and golf tournaments were held. There were tours of Chicago's neighborhoods, churches, theaters, markets, and gardens and a number of tours that focused on the architecture of Frank Lloyd Wright, Louis Sullivan, and many contemporary architects of the city. Special tours of the Art Institute of Chicago, the Museum of Science and Industry, and other museums were arranged, and there was a sunset cruise of the Chicago River and lakefront.

# Meeting of the Board of Trustees

The Board of Trustees met in regular session on Sunday, May 10.

# Meetings of the Assembly

The Assembly met on Friday, Saturday, and Sunday, May 8, 9, and 10.

ELISSA P. BENEDEK, M.D. Secretary, American Psychiatric Association

# 1986–1987 Annual Report of the American Board of Psychiatry and Neurology, Inc.

# Composition of the Board

At its business meeting on Nov. 22, 1986, the American Board of Psychiatry and Neurology (ABPN) elected the following officers, who began their terms on Jan. 1, 1987: Dr. Robert A. Fishman, President; Dr. John A. Talbott, Vice-President; Dr. Robert Michels, Secretary; Dr. Jack P. Whisnant, Treasurer; and Dr. Elliott L. Mancall, Executive Committee Member-at-Large.

Dr. James H. Shore (Professor and Chairman, Department of Psychiatry, University of Colorado School of Medicine), nominated by the American Psychiatric Association, was elected to a 4-year term on the Board. Dr. Carolyn Robinowitz completed her second 4-year term on the Board in December 1986. Dr. Layton McCurdy, nominated by the APA Board of Trustees, was reelected to serve a second 4-year term as Director. Dr. John F. McDermott, Jr., nominated by the APA Section Council to the AMA, was reelected to serve a second 4-year term as Director. Dr. Ludwig Gutmann (Professor and Chairman, Department of Neurology, West Virginia Medical Center), nominated by the American Neurological Association, was elected to a 4-year term on the Board to succeed Dr. Desmond O'Doherty. Drs. Elliott L. Mancall, N. Paul Rosman, and Jack P. Whisnant, nominated by the American Academy of Neurology, were each reelected to serve a second 4-year term on the Board. The names of the 1987 ABPN Directors follow; those serving second 4-year terms are not eligible for reelection.

Nominated by the American Medical Association: Dr. M.J. Martin (term expires December 1987); Dr. John F. McDermott, Jr. (second term expires December 1990); and Dr. William L. Webb, Jr. (second term expires December 1989).

Nominated by the American Psychiatric Association: Dr. John A. Talbott (second term expires December 1987); Dr. Robert Michels (second term expires December 1989); Dr. Layton McCurdy (second term expires December 1990); Dr. Gary J. Tucker (term expires December 1988); and Dr. James H. Shore (term expires December 1990).

Nominated by the American Neurological Association: Dr. William E. Bell (term expires December 1987); Dr. J. Donald Easton (term expires December 1988); Dr. Stuart A. Schneck (term expires December 1989); and Dr. Ludwig Gutmann (term expires December 1990).

Nominated by the American Academy of Neurology: Dr. Elliott L. Mancall (second term expires December 1990); Dr. N. Paul Rosman (second term expires December 1990); Dr. Jack P. Whisnant (second term expires December 1990); and Dr. Robert A. Fishman (second term expires December 1988).

Effective January 1986, Stephen C. Scheiber, M.D., assumed the position of ABPN Executive Secretary.

# Credentials

The Board took the following actions related to credentials:

- 1. As a parent group of the Residency Review Committee for Psychiatry, approved the revised "Essentials of Accredited Residencies" for psychiatry, to be effective July 1, 1987.
- 2. As a parent group of the Residency Review Committee for Neurology, approved the revised "Essentials of Accredited Residencies" for neurology, to be effective Jan. 1, 1988.
- cies" for neurology, to be effective Jan. 1, 1988.
  3. Approved the "Essentials of Accredited Residencies" for child neurology, to be effective Jan. 1, 1988.
- 4. Approved the "Essentials of Accredited Residencies" for child psychiatry.
- 5. Reaffirmed its policy, effective July 1, 1988, whereby physicians entering psychiatry residency at the second postgraduate year level must have obtained credit for the first postgraduate year from

TABLE 1. Candidates for ABPN Part I (Written) Examination, 1982–1987

	Number of Candidates								
Physician Status	1982	1983	1984	1985	1986	1987			
Met requirements Accepted	2,117	2,187	2,029	2,506	2,703	2,649			
examination Appeared for	2,008	2,064	1,929	2,409	2,574	2,477			
examination	1,824	1,849	1,738	2,167	2,3(1	2,255			

a program approved by the Accreditation Council for Craduate Medical Education.

6. Approved the policy whereby all licensing and training requirements must be met before application for examination, except for residents who complete training after Sept. 1 but before Oct. 1, who may submit applications by the Sept. 1 deadline.

# Examinations

Part I. At the part I (written) examination on March 31, 1987, 1,670 psychiatrists were examined; 921 (55%) passed and 749 (45%) failed. A total of 585 neurologists were examined; 336 (57%; passed and 249 (43%) failed. Table 1 contains the numbers of candidates in each year from 1982 to 1987. The next part I examination is on April 12, 1988.

Part II. At the 1986 part II (oral) examinations held in Seattle (Feb. 23–25), Milwaukee (June 9–11), and Philadelphia Nov. 23–25), 1,426 psychiatrists, 427 neurologists, and 63 child neurologists were examined. For statistics on these examinations, see table 2. The examination sites for 1987 are Houston (Jan. 11–13), Los Angeles (April 26–28), and New York (Nov. 15–17).

# Child Psychiatry

The members of the 1986 Committee on Certification on Child Psychiatry were Dr. John Schowalter, Chair; Dr. Richard I Cohen, Vice-Chair; Dr. Donald S. Gair, Secretary-Treasurer; Dr. Joseph Fischoff; Dr. Peter E. Tanguay; Dr. Joel P. Zrull; and Dr. 1718 F. Litt, member from the American Board of Pediatrics.

At its Sept. 7–9, 1986, examination in Boston, the committee examined 220 candidates. The number of passing candidates was 131 (59%). Of the remaining 89 candidates, 40 (18%) conditioned the examination and 49 (23%) failed.

In 1986 the Committee on Certification in Child Psychiatry took the following significant actions:

- 1. Effective with the Sept. 18–20, 1987, examination in Minneapolis, the committee approved a Saturday/Sunday examination format. It is believed the change will be cost effective Hospital facilities have indicated that the weekend format will alleviate logistical problems associated with weekday examinations.
- logistical problems associated with weekday examinations.

  2. The committee approved the "Essentials of Accrecited Residencies" for child psychiatry.
- 3. Dr. William H. Sack was elected to succeed Dr. Richard Cohen as a committee member on expiration of his term on Dec. 31, 1986.
- 4. Dr. John Schowalter was reelected Chair of the committee for the year beginning Jan. 1, 1987.
- 5. Dr. Peter E. Tanguay was elected Vice-Chair of the committee for the year beginning Jan. 1, 1987.
- 6. Dr. Donald S. Gair was reelected Secretary-Treasurer of the committee for the year beginning Jan. 1, 1987.

TABLE 2. Performance of Physicians Who Took ABPN Part II (Oral) Examinations in 1986

									Gradu	ates in U.S	and Ca	nada	F	oreign Gra	duates	
Examination	Tot	al	Psych	iatry	Neur	ology		hild rology	Num- ber	Number Reex-	Tot	al	Num- ber	Number Reex-	To	otal
Results	N	%	N	%	N	%	N	%	New	amined	N	%	New	amined	N	%
Passed and	1 125	50	015	-7	274	<i>C</i> 4	27	57	743	210	0.61	<b>~</b> 0	115	40	174	22
certified Failed	1,125 791	59 41	815 611	37 43	274 153	64 36	36 27	57 43	743 290	218 156	961 446	68 32	115 146	49 199	164 345	32 68
Total	1,916	100	1,426	100	427	100	63	100	1,033	374	1,407	100	261	248	509	100

- 7. Dr. John Schowalter, as Chair and representative of the committee, attended the July 1986 Conference on Sub-Specialty Certification hosted by ABPN in Snowmass, Colo.
- 8. The committee approved changing its name to the "Committee on Certification in Child and Adolescent Psychiatry" and submitted its recommendation to the Board for ratification.
- 9. The committee approved combining the preschool and grade school sections of the examination into one section named "Preschool/Grade School." The change was effective with the 1986 examination.

# Board Decisions and Items of Interest

Since its last annual report the ABPN has taken the following actions:

- 1. Approved the Board office move to 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015, effective June 15, 1987. The new telephone number will be (312) 945-7900.
- 2. Contracted with the American Board of Medical Specialties to study the reliability of the part II examination. Interexaminer consistency and the stability of grading over a 1-year period, 1986, will be reviewed in the study.
- 3. Ratified its membership as one of five parent groups of the Neurology Intersociety Liaison.
- 4. Approved definitions for all specialties, which will be included in the American Board of Medical Specialties' informational brochure *Definition of a Specialist*.
- 5. Approved a definition for the ABPN Self-Indemnification Fund.
- 6. Considered greater involvement in developing an in-service examination for neurology residents, as proposed by the Intersociety Committee on Neurological Resources.
- 7. Withdrew permission to issue certificates of special qualification in critical care medicine for neurologists in conjunction with an examination administered by the American Board of Internal Medicine.
- 8. Instituted two levels of feedback for adult and child neurology candidates who receive negative determinations in the part II examination (appendix 1).
- Revised the appeal procedure for negative determinations regarding the part II neurology examination (appendix 1).
- 10. Appointed Dr. Marc Hollender to act as historian in updating the Board's records.
- 11. Elected to continue submitting the names of newly certified physicians to Marquis Who's Who, Inc., for publication in its *Directory of Medical Specialists*, as well as to the American Board of Medical Specialties.
- 12. Hosted the Conference on Sub-Specialty Certification in July 1986, which was attended by six representative groups: American Board of Forensic Psychiatry, American Society for Adolescent Psychiatry, American Association for Geriatric Psychiatry, American Academy of Psychiatrists in Alcoholism and Addictions, the APA Committee on Administrative Psychiatry, and the American Psychoanalytic Association.
- 13. Approved continuing dialogue, through an APBN representative, with the American Association of Electrophysiology and Electrodiagnosis regarding subspecialty certification.
- 14. Approved an application by the American Board of Emergency Medicine to issue Certificates of Added Qualification in Critical Care Medicine.

- 15. Revised its policy statement on Board review courses whereby a physician who participates in a Board review course is excluded from examining for 12 months (appendix 2).
- 16. Agreed not to pursue dual certification in neurology and internal medicine.
- 17. Approved a revised travel policy for the Committee on Certification in Child Psychiatry.
- 18. Approved the policy that a passing grade on the part I examination dated March 1987 or thereafter is valid for 6 years or three attempts to complete the part II examination successfully, whichever comes first. This policy took effect March 1, 1987.
- 19. Approved a modification of the fee schedule that reflects a merging of the application fee and the part I fee (apendix 3). The change took effect March 1, 1987.
- 20. Endorsed a position statement on subspecialty certification (appendix 4).

# APPENDIX 1. Appeal Procedure for Negative Determinations Regarding ABPN Part II Neurology Examination

A failing grade on a Part II Neurology Examination is considered a "negative determination." A candidate will be advised of which sections were failed in the initial grade letter sent from the Board office. This is considered the first level of feedback. A candidate who receives a negative determination may appeal by complying with the following procedures:

- 1. Within thirty (30) days after date of notice of a negative determination, the unsuccessful candidate may, by writing, indicate his/her request for a preliminary review of this negative determination. After such request, the candidate will be provided information concerning his/her performance. This is considered the second and final level of feedback provided to the candidate. Fee for this preliminary review will be \$100.00. This fee must be received before information is provided.
- 2. Following this, the unsuccessful candidate may, by writing, indicate his/her request for a formal appeal to the Neurology Review Committee. Information tending to rebut the negative determination should be forwarded with three additional copies for members of the Review Committee, along with the fee, and must be received within fifty-five (55) days after date of notice of a negative determination. No additional feedback will be provided to the candidate. The fee for this formal appeal will be equal to the candidate's reexamination fee and is separate from the fee in (1) above.
- 3. The Neurology Review Committee will review the written information required in (2) above and the candidate will be notified in writing of the decision. If the Review Committee decides to affirm the negative determination in question, the candidate has the right to appeal the decision. Notice of intent to appeal the Review Committee's decision and request to appear personally with or without counsel before the Review Committee must be received within thirty (30) days after date of notice of the Committee's original decision. At any such appearance, the candidate will be given the opportunity to present his/her position. A transcript of the proceedings will be kept. The Review Committee will not be bound by technical rules of evidence usually employed in legal proceedings, but may consider any evidence it deems appropriate. If the candidate requests to appear personally with or without counsel before the Review Committee, and subsequently, without good cause, fails to appear at the proceeding or advises the Review Committee in writing less than

ten (10) days before the scheduled date of the proceeding that he/she cannot or will not appear at the proceeding, the Review Committee may decide to notify the candidate in writing that no other opportunity for a personal appearance before the Review Committee shall be provided.

- 4. If the candidate appeals the decision of the Review Committee to the Board, written notice of this must be received within twenty (20) days from the date of the letter of the Review Committee's decision. The Board will review all of the evidence considered by the Review Committee; however, the Board will not consider any evidence that was not presented to the Review Committee. If the Board disagrees with the decision of the Review Committee, it may reverse the decision or remand the matter to the Review Committee for further consideration with precise instructions as to the basis of such reconsideration. The candidate will be informed in writing of the Board's decision which, in all events, will be final and binding on the Board and on the candidate.
- 5. All notices or other correspondence directed to the Review Committee or to the Board should be sent to the following address: American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

# APPENDIX 2. ABPN Policy Regarding Board Examination Review Courses (revised July 1986)

Several institutions across the country provide review courses that are specifically offered as preparation for the Part II ABPN Board Examination. Other courses, while not explicitly referring to the ABPN Part II Examination, are easily construed as being similar review courses. Problems arise when persons involved in these courses subsequently appear as examiners in the Part II Examination. The Board is reaffirming its policy concerning the appearance of conflict of interest in this situation.

The Board policy states that any individual who participates in a review course which is publicized as being a Board review course, or in a course which could be construed as a Board review course, should not participate in any Part II Examination for at least 12 months subsequent to the course. If there is any question as to whether a course might be construed as an ABPN review, please contact the Board Director who has invited you to examine for a decision. This policy is in no way intended to interdict normal

educational activities where there is no explicit or implied indication that the educational activity is designed to aid a candidate in passing an ABPN Part II Examination.

# APPENDIX 3. Revised ABPN Fee Schedule for 1987

Part I examination fee	\$450
Part I reexamination fee	250
Part II examination fee	350
Part II reexamination fee, failure of minor	250
Part II reexamination fee, failure of major	350
Part II reexamination fee, failure of major and minor	350

# APPENDIX 4. ABPN Position Statement on Subspecialty Certification (adopted January 1987)

There has been a growing dialogue concerning the desirability of formal recognition of subspecialties in American Psychiatry. The A.P.B.N. intends to participate actively in this dialogue. It sees its primary functions as:

- 1. Maintaining contact with various interested groups both within and outside of the profession, encouraging their consideration of the issues,
- 2. Periodically reviewing the desirability of developing formal certification in the various subspecialties, employing the guidelines outlined by the American Board of Medical Specialties, including the nature of the knowledge base, the adequacy of training programs. the social organization of the subspecialty discipline, and the impact of the subspecialty decision on the subspecialty, the protession in general, and the public,
- 3. Communicating with the profession concerning both these criteria and the results of periodic appraisals, and
- 4. If appropriate, developing subspecialty certification procedures.

The A.B.P.N. views the decision concerning subspecialties as a matter for wide discussion. The Board's special decisions regarding certification should be made after a careful assessment of the profession's development. Of course, individual Directors of the Board may in their other roles, participate in the dialogue as active advocates.

# Position Statement on AIDS

This statement was drafted by the Task Force on Psychiatric Aspects of AIDS. It was passed by the Board of Trustees in December 1986 and by the Assembly in May 1987.

# Introduction

The Human Immunodeficiency Virus (HIV) is thought to cause the Acquired Immune Deficiency Syndrome (AIDS), AIDS Related Complex (ARC), and probably other disease states. In the following statement the term HIV disease is used to refer to the entire range of clinical conditions in adults and children which may be produced by this virus

# Position Statement

The American Psychiatric Association asserts that:

- 1. Psychiatrists should work actively and effectively to counteract inappropriate reactions to HIV disease in their communities and professional activities.
- 2. Psychiatrists have a responsibility to educate themselves, their patients, and their communities with regard to the neuropsychiatric and psychosocial aspects of HIV disease including its biological and psychiatric clinical manifestations, the psychosocial reactions to the illness and the appropriate treatment modalities available to patients. To this end, psychiatrists should integrate their efforts with those of other medical disciplines and work conjointly with them.
  - 3. Psychiatrists and other physicians have an obligation to be-

come educated about the legal and ethical aspects of HIV disease and to help patients make informed and rational decisions, for example, in the areas of confidentiality, privacy, informed consent, living wills, and durable powers of attorney.

- 4. Educational activities should be undertaken to prevent the spread of HIV disease.
- 5. Activities which attempt to reduce risk-associated practices should be based upon knowledge and understanding of the complex and sensitive nature of this effort.
- 6. It actively supports efforts to eliminate medical, psychiatric, social, economic, occupational, legal, educational, and other forms of discrimination which is based on the fear of HIV disease.
- 7. The confidentiality of persons undergoing HIV serologic testing for clinical or research purposes should be protected, and all information obtained including identifying data and test results should be used only for the purposes explicitly stated in the informed consents and releases of information. When testing is performed for clinical or research purposes, attention to the psychiatric implications must be considered pre- and post-testing and the possible adverse consequences of serologic testing be explicitly stated in the informed consent.
- 8. Knowledge of serologic test results may have beneficial or adverse psychiatric effects. Currently, there is insufficient information to support the assumption that knowledge of one's serologic status necessarily leads to risk-reducing behavior change. Research is needed to clearly identify the psychiatric ramifications of serologic HIV testing and to define appropriate criteria for its use.
- 9. There is urgent need for research on the psychiatric presentations and complications of HIV infection.

# Position Statement on HIV-Related Discrimination

This statement was drafted by the Task Force on Psychiatric Aspects of AIDS. In October 1986 the joint Reference Committee recommended a few editorial changes, which were incorporated into the draft sent to the Assembly. The Assembly approved the position statement in November 1986, as recommended by the joint Reference Committee, and the Board of Trustees approved the statement in December 1986.

The American Psychiatric Association (APA) recognizes that

individuals may develop and maintain anxiety and/or unjustified fears such as have occurred in reaction to HIV related issues.

These fears should not be the basis of discriminatory actions nor prevent access to medical care, housing, public transportation, employment, education, and life, medical, or disability insurance.

Specifically, the APA considers it a priority to educate its members, other health care professionals, and the general public to reduce these reactions to HIV conditions.

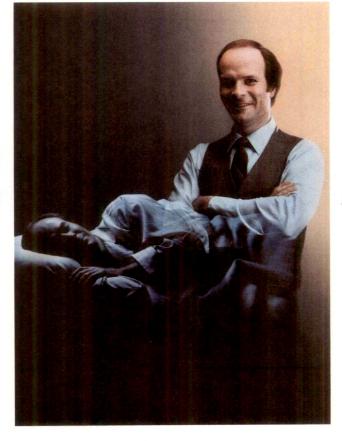
The APA shall respond to instances in which such reactions to HIV conditions lead to discriminatory practices or become the basis of unjustified public policy.

<sup>&</sup>lt;sup>1</sup>The task force included Stuart E. Nichols, Jr., M.D. (chairperson), Francisco Fernandez, M.D., Marshall Forstein, M.D., James J. Strain, M.D., James W. Dilley, M.D. (consultant), Harold Ginzburg, M.D. (consultant), Melvyn R. Haas, M.D. (consultant), Alexandra Beckett, M.D. (corresponding member), Robert Cabaj, M.D. (corresponding member), Joyce Johnson, M.D. (corresponding member), David Kessler, M.D. (corresponding member), David Ostrow, M.D. (corresponding member), Rafael J. Tavares, M.D. (corresponding member), and Dianne Wolcott, M.D. (corresponding member).



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**INDICATIONS AND USAGE:** HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

**CONTRAINDICATIONS:** Patients with known hypersensitivity to this drug or other begandiagenines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

**WARNINGS:** Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

neous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam. hence increased clinical observation and consideration of dosage reduction may be appropriate. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

**ADVERSE REACTIONS:** During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo	
Number of Patients	1003	997	
% of Patients Reporting:			
Central Nervous System			
Drowsiness	14.0	6.4	
Headache	9.7	8.4	
Dizziness	7.8	3.1	
Nervousness	5.2	4.5	
Lightheadedness	4.9	0.9	
Coordination Disorder/Ataxia	4.6	0.8	
Gastrointestinal			
Nausea/Vomiting	4.6	3.7	

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodia-zepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment protracted, periodic blood counts, urinalysis and blood chemistry
analyses are addisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

**DRUG ABUSE AND DEPENDENCE:** Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

**OVERDOSAGE:** Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

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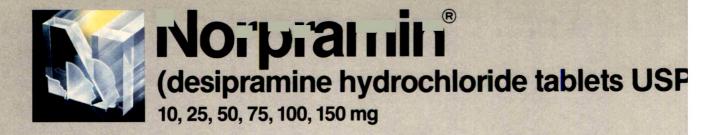
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The fastest growing antidepressant in the U.S.A.

# Now after 20 years, the antidepressant most widely prescribed by psychiatrist

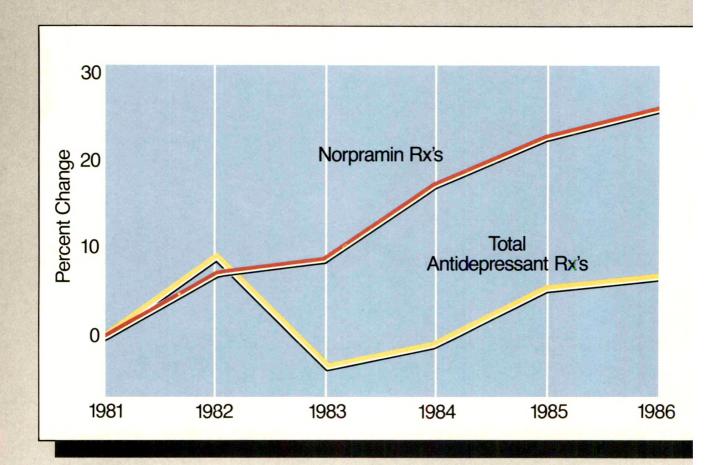


Figure 1.

The red line tracks the percent change in Norpramin prescriptions; the yellow line represents the percent change in total prescription activity the antidepressant market (results of nationwide independent survey).

# **Merrell Dow**

# Vhen a precise dosage titration and he added flexibility of once daily, single ablet dosing are desirable

"...selection of pharmacological agents that can be prescribed once or twice a day will improve patient compliance." 1

Norpramin allows you to choose							
This	C	or T	his				
25 mg tid		75 mg	qd 🕚				
25 mg qid	0000	100 mg	qd 👵				
50 mg tid		150 mg	qd 🐝				

the fastest growing antidepressant in the U.S.A. a 20-year record of efficacy in relieving the symptoms of depression a clinical profile well defined over time the choice of a once or twice daily single tablet dosage, and the added flexibility of six different dosage strengths



# Norpramin

# (desipramine hydrochloride tablets USF

10, 25, 50, 75, 100, 150 mg

# Dosage Flexibility

Convenient choice of six tablet strengths and once daily or divided dosage schedule allows titration to individual response.



10 mg



25 mg



50 ma



75 ma



100 mg



150 mg

# The antidepressant most widely prescribed by psychiatrists

# Norpramin<sup>®</sup>

(desipramine hydrochloride tablets USP)

# AVAILABLE ONLY ON PRESCRIPTION

**Brief Summary** 

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic anti-depressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the reuptake of these substances from the synapse in the central nervous system.

uptake of these substances vous system. Evidence indicates that the secondary amine tricyclic anti-depressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on

Evidence Indicates that run escondary amine tricyclic antidepressants, including Norpramin, may have greater activity in 
blocking the re-uptake of norepinephrine. Tertiary amine tricyclic 
antidepressants, such as amitriptyline, may have greater effect on 
serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine 
oxidase (MAO) inhibitor and does not act primarily as a central 
nervous system stimulant. It has been found in some studies to 
have a more rapid onset of action than imigramine. Earliest 
therapeutic effects may occasionally be seen in 2 to 5 days, but 
full treatment benefit usually requires 2 to 3 weeks to obtain. 
INDICATIONS: Norpramin (desipramine hydrochloride) is indicated 
for reliet of symptoms in various depressive syndromes, especially endogenous depression. 
CONTRAINDICATIONS: Desipramine hydrochloride should not be 
given in conjunction with, or within 2 weeks of, treatment with an 
MAO inhibitor drug; hyperpyretic crises, severe convulsions, and 
death have occurred in patients taking MAO inhibitors and tricyclic 
antidepressants. When Norpramin (desipramine hydrochloride) is 
substituted for an MAO inhibitor, at least 2 weeks should elapse 
between treatments. Norpramin should then be started cautiously 
and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have 
shown prior hypersensitivity to the drug. Cross sensitivity 
between this and other dibenzazepines is a possibility. 
WARNINGS: 1. Extreme caution should be used when this drug is 
given in the following situations: a. In patients with cardiovascular 
disease, because of the possibility of conduction defects arrhythmias, d. In patients with a history of urinary retention or glaucoma, 
because of the possibility of cardiovascular toxicity, including 
arrhythmias, d. In patients with a history of urinary retention or glaucoma, 
because this drug has been shown to lower the seizure threshold.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since sui-

cide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind: if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. 2 If serious adverse effects occur, dosage should be reduced or treatment should be altered. 3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates. 4. The drug may cause exacerbation of psychosis in schizophrenic patients. 5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anti-cholinergic or sympathomimetic drugs. 6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. 7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. 8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzolazepines (e.g., chloridiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. 9. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking designamine hydrochloride. 10. Both elevation and lowering of blood sugar levels have been reported. 11. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evid

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is

Gardiovascular, hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric, confusional states (especially in the elderly) with halucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic, purchases, finaling, page 1878.

<u>Neurologic</u> numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extra-pyramidal symptoms; seizures; alteration in EEG patterns; tenthological symptoms.

tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adentits; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dialation of urinary tract. Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs. Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia. Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tonque.

Endocrine: gynecomastia in the male, breast enlargemen galactorrhea in the female; increased or decreased libido, i tence, testicular swelling; elevation or depression of blood

Other: jaundice (simulating obstructive), altered liver fund unter: jaundice (simulating obstructive), aftered liver function weight gain or loss; perspiration, flushing, urinary frequency, turia; parotid swelling, drowsiness, dizziness, weakness tatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, a cessation of treatment after prolonged therapy may produce say headache, and making.

cessation of treatment after prolonged therapy may produce sea, headache, and malaise

DOSAGE AND ADMINISTRATION: Not recommended for uchildren. Lower dosages are recommended for elderly pat and adolescents. Lower dosages are also recommended to patients compared to hospitalized patients, who are closely sivised. Dosage should be initiated at a low level and increase coording to clinical response and any evidence of intolerations of the production of the properties of the programment of the programment of the production of the p a period of time and should be at the lowest dose that will ma

a period of time and should be at the lowest dose that will mai remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per In more severely ill patients, dosage may be further incre gradually to 300 mg/day if necessary. Dosages above 300 m are not recommended.

Dosage should be initiated at a lower level and incre according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg st generally be initiated in hospitals, where regular visits by physician, skilled nursing care, and frequent electrocardiog (ECG's) are available.

The best available evidence of impending toxicity from very doses of Norpramin is prolongation of the QRS or OT interva the ECG. Prolongation of the PR interval is also significant less closely correlated with plasma levels. Clinical symptor intolerance, especially drowsiness, dizziness, and postural tension, should also alert the physician to the need for redu in dosage. Plasma desipramine measurement would cons the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a staily dose.

Maintenance therapy may be given on a once-daily schedu.

Initial therapy may be administered in divided doses or a s daily dose.

Maintenance therapy may be given on a once-daily schedu patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and ger dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and incre according to tolerance and clinical response to a usual maxi of 100 mg daily. In more severely ill patients, dosage ma further increased to 150 mg/day. Doses above 150 mg/day ar recommended in these age groups.

Initial therapy may be administered in divided doses or a s daily dose.

Minima therapy may be given on a once-daily schedu daily dose.

Maintenance therapy may be given on a once-daily schedu patient convenience and compliance.

OVERODSAGE: See prescribing information for a discussion symptoms and treatment of overdose.

Product Information as of January, 1985

MERRELL DOW PHARMACEUTICALS INC. Subsidiary of The Dow Chemical Company Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

(Continued from page A14)

Samuel O. Thier, M.D., President, 2101 Constitution Ave., N.W., Washington, DC 20418; 202-334-3300.

October 21–23, annual conference, New York State Association of Psychosocial Clubs, Poughkeepsie, N.Y. Contact Conference Coordinator, Ellen Del Colle, Mental Health Association in Dutchess County, Inc., 230 North Rd., Poughkeepsie, NY 12601; 914-485-9700, ext. 544.

October 21–25, annual meeting, American Academy of Child Psychiatry, Washington, D.C. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-966-7300.

October 22–25, annual meeting, Academy of Psychosomatic Medicine, Las Vegas. Contact Sanford J. Hill, Executive Director, 70 West Hubbard St., Suite 202, Chicago, IL 60610; 312-644-2623.

October 23–26, annual meeting, Society for Traumatic Stress Studies, Baltimore. Contact STSS, P.O. Box 2106, Dayton, OH 45401-2106; 513-278-1905.

October 25–28, annual meeting, American Council on Education, Washington, D.C. Contact Robert H. Atwell, President, One Dupont Circle, N.W., Suite 801, Washignton, DC 20036; 212-939-9300.

October 25–29, Institute on Hospital & Community Psychiatry, Boston. Contact Susan Lash, Programs Assistant, American Psychiatric Association, 1400 K St., N.W., Washington, DC 20005; 202-682-6173.

October 27–30, international conference, Critical Risk—Quality Care: Adolescents in Secure Settings, Thistletown Regional Centre for Children and Adolescents, Toronto. Contact Dr. Roberta Roberts, Thistletown Regional Centre, 51 Panorama Ct., Rexdale, Ontario M9V 4L8, Canada; 416-741-1210.

October 28–30, annual meeting, National Academy of Neuropsychologists, Chicago. Contact Antonio Puente, Ph.D., Dept. of Psychology, University of North Carolina, Wilmington, NC 28403; 919-395-3812.

October 29-November 1, annual conference, American Association for Marriage & Family Therapy, Chicago. Contact Diane Sollee, M.S.W., Conference Director, AAMFT, 1717 K St., N.W., #407, Washington, DC 20006; 202-429-1825.

October 30-November 1, annual meeting, Epilepsy Foundation of America, Alexandria, Va. Contact William M. McLin, Executive Vice-President, 4351 Garden City Dr., Suite 406, Landover, MD 20785; 301-459-3700.

October 30-November 1, annual conference, North American Riding for the Handicapped Association, Inc., New

Orleans. Contact Eva Hofmann, NARHA, 111 East Wack.r Dr., Chicago, IL 60601; 312-644-6610.

October 31-November 4, annual meeting, Southern Medic l Association, San Antonio, Tex. Contact William J. Ranie, Executive Vice-President, P.O. Box 190088, Birmingham, AL 35219-0088; 205-945-1840.

October 31-November 5, annual meeting, American Academy of Pediatrics, New Orleans. Contact M. Harry Jenniso , M.D., Executive Director, P.O. Box 927, Elk Grove Villag., IL 60007; 312-228-5005.

# **NOVEMBER**

November 1-5, International Congress on Suicide, Universidade Federal do Estado de Rio de Janeiro, Rio de Janeiro. Contact Luis Vasquez, M.D., MILA, 38760 Northwood D., Wadsworth, IL 60083; 312-249-1900, 800-367-7378.

November 2–5, annual meeting, American College of Emergency Physicians, San Francisco. Contact Collin C. Rorr v, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-659-0911.

November 5–7, 11th National Conference on Correctional Health Care, National Commission on Correctional Health Care and American Correctional Health Services Assoc, Chicago. Contact NCCHC, 2000 North Racine, Suite 3500, Chicago, IL 60614; 312-528-0818.

November 6-7, The Many Faces of Late-Life Depression, Boston Society for Gerontologic Psychiatry, Boston. Contact Sandra White, BSGP, 64 Hancock Ave., Newton, MA 02159; 617-527-5550.

November 6–9, annual meeting, National Rehabilitation Assoc., New Orleans. Contact David L. Mills, Executive Director, 633 S. Washington St., Alexandria, VA 22314; 703-836-0850.

November 7–12, annual meeting, Association of American Medical Colleges, Chicago. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, DC 20036; 202-828-0400.

November 8-13, annual meeting, Association of Military Surgeons of the United States, Las Vegas. Contact Lt. General Max B. Bralliar, Executive Director, P.O. Box 10-4, Kensington, MD 20895; 301-933-2801.

November 10–13, annual meeting, Association for Medical Education and Research in Substance Abuse, Rockville, Md. Contact AMERSA Conference Coordinator, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912; 401-863-1109.

# Books Received

- The Subtle Seductions: How to Be a "Good Enough" Parent, by Gertrude Blanck, Ph.D. Northvale, N.J., Jason Aronson, 1987, 176 pp., \$17.50.
- Psychological Maltreatment of Children and Youth, by Maria R. Brassard, Robert Germain, and Stuart N. Hart. New York, Pergamon Press, 1987, 273 pp., \$45.00.
- Antimanics, Anticonvulsants and Other Drugs in Psychiatry, edited by Graham D. Burrows, Trevor R. Norman, and Brian Davies. Amsterdam, Elsevier (New York, Elsevier Scientific Publishing Co., distributor), 1987, 438 pp., \$133.25.
- Nostalgia and Sexual Difference: The Resistance to Contemporary Feminism, by Janice Doane and Devon Hodges. New York, Methuen, 1987, 164 pp., \$25.00; \$9.95 (paper).
- Clinimetrics, by Alvan R. Feinstein, M.D. New Haven, Yale University Press, 1987, 265 pp., \$25.00.
- The Unquiet Dead: A Psychologist Treats Spirit Possession, by Edith Fiore, Ph.D. Garden City, N.Y., Dolphin (Doubleday & Co.), 1987, 177 pp., \$15.95.
- Study Guide and Self-Assessment for The American Psychiatric Press Textbook of Neuropsychiatry, by Michael D. Franzen, Ph.D., and Mark R. Lovell, Ph.D. Washington, D.C., American Psychiatric Press, 1987, 219 pp., \$20.00 (paper).
- The American Psychiatric Press Textbook of Neuropsychiatry, edited by Robert E. Hales, M.D., and Stuart C. Yudofsky, M.D. Washington, D.C., American Psychiatric Press, 1987, 463 pp.,
- Living High: Daily Marijuana Use Among Adults, by Herbert Hendin, M.D., Ann Pollinger Haas, Ph.D., Paul Singer, M.D., Melvyn Ellner, Ph.D., and Richard Ulman, Ph.D. New York, Human Sciences Press, 1987, 180 pp., \$24.95.
- Adolescent Runaways: Causes and Consequences, by Mark-David Janus, Arlene McCormack, Ann Wolbert Burgess, and Carol Hartman. Lexington, Mass., Lexington Books (D.C. Heath & Co.), 1987, 148 pp., \$25.00; \$12.95 (paper).
- Men in Feminism, edited by Alice Jardine and Paul Smith. New
- York, Methuen, 1987, 285 pp., \$29.95; \$11.95 (paper).

  Treating Childhood and Adolescent Obesity, by Daniel S. Kirschenbaum, William G. Johnson, and Peter M. Stalonas, Jr. New York, Pergamon Press, 1987, 146 pp., \$21.50; \$11.95

- (paper).
- Anxiety, edited by D. F. Klein with A. J. Fyer, J. M. Gorman, and M.R. Liebowitz. Basel, Karger, 1987, 192 pp., \$65.50.
- Computer Applications in Psychiatry, by Jonathan D. Lieff, M.D. Washington, D.C., American Psychiatric Press, 1987, 414 pp., \$32.00.
- Caring for Your Parents: A Sourcebook of Options and Solutions for Both Generations, by Helene MacLean. Garden City, N.Y., Doubleday & Co., 1987, 363 pp., \$12.95 (paper).
- Critical Issues in Psychology, Psychiatry, and Physiology: A Memorial to W. Horsley Gantt, edited by F. J. McGuigan and Thomas A. Ban. New York, Gordon and Breach Science Publishers, 1987, 379 pp., \$49.00.
- The Chronic Mental Patient/II, edited by W. Walter Menninger, M.D., and Gerald T. Hannah, Ph.D. Washington, D.C., American Psychiatric Press, 1987, 242 pp., \$28.00.
- Nine-Year-Olds Grow Up: A Follow-Up Study of Schoolchildren, by Sheila Mitchell. London, Tavistock, and New York, Methuen, 1987, 177 pp., \$49.95.
- Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives, edited by Marian Osterweis, Arthur Kleinman, and David Mechanic, Institute of Medicine Committee on Pain, Disability, and Chronic Illness Behavior. Washington, D.C., National Academy Press, 1987, 292 pp., \$24.95 (paper).

  Overcoming Depression, by Demitri F. Papolos, M.D., and Janice
- Papolos. New York, Harper & Row, 1987, 305 pp., \$18.95.
- Moving Into Adolescence: The Impact of Pubertal Change and School Context, by Roberta G. Simmons and Dale A. Blyth. New York, Aldine de Gruyter, 1987, 422 pp., \$52.95.
- Maternal Depression and Infant Disturbance, edited by Edward Z. Tronick and Tiffany Field. San Francisco, Jossey-Bass, 1986, 82 pp., \$9.95 (paper).
- Handbook of Adolescent Psychology, by Vincent B. Van Hasselt and Michel Hersen. New York, Pergamon Press, 1987, 471 pp.,
- Szenen Einer Psychiatrie: Streitschrift Gegen die Konzentration des Wahnsinns und fur Mehr Psychosoziale Kultur, by Bernhard Wagner. Konstanz, W. Germany, Verlag Rainer Magulski, 1987, 207 pp., no price listed (paper).

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Papers		
		knowledge about schizophrenia: a arrier, S. Watts, C. Vaughn, J.S. Bamrah
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Monitoring the occur and J. Lambourn	rence and duration of	electroconvulsive fits. P. Barrington
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		phrenia in a high risk sample. R.A.
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# CONDITIONS OF APPOINTMENT

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Professors medically qualified with medical science appointments

KD.1140-1300 (8 increments)

Professors non-medically qualified

KD.1070-1230 (8 increments)

Associate Professors with clinical appointments

KD. 989-1149 (8 increments)

Associate Professors medically qualified with medical science appointments

KD. 932-1092 (8 increments)

Associate Professors non-medically qualified

KD. 875-1035 (8 increments)

Assistant Professors with clinical appointments

KD. 768- 928 (8 increments)

Assistant Professors medically qualified with medical science appointments

KD. 724-884 (8 increments)

Assistant Professors non-medically qualified

KD. 680- 840 (8 increments)

Social allowance: In addition to the above salary, social allowance is paid in accordance with the rules and regulations of the University.

Clinical supplements: In addition to the above University salaries there will be monthly clinical supplement paid by the Ministry of Public Health for 10 months a year to medical school staff with clinical service commitments. These are

> KD. 450. Professor and Chairman KD. 400. Professor Associate Professor KD. 300. KD. 200. Assistant Professor

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Housing: Suitably furnished, air-conditioned accommodation, electricity and water free of charge.

Medical Care: Free, comprehensive treatment is available in Kuwait under the State Health Service.

Travel: Air tickets are provided from the country of recruitment for the appointee, spouse and up to 3 dependent children under 20 years. Thereafter, return air tickets are issued annually to the country of citizenship or permanent residence. On termination of contract, air tickets are provided to the country of recruitment. A baggage and freight allowance is also provided.

Vacation: 60 days paid annual leave and various national holidays.

Education: This is provided free in State Schools where the instruction is in Arabic. Staff who have to send their children to non-Arabic schools in Kuwait will have the tuition fees of up to a maximum of three children met by the University.

Taxation: There is no income tax in Kuwait. Currency is transferable without restriction.

# **METHOD OF APPLICATION:**

Curriculum vitae in duplicate which should include the names of referees, personal particulars, qualifications with dates, career history, teaching experience, research accomplishments and appropriate clinical experience should be sent to the DIRECTORY OF PLANNING AND ACADEMIC STAFF RECRUITMENT, FACULTY OF MEDICINE, UNIVERSITY OF KUWAIT, HEALTH SCIENCE CENTRE, P.O. BOX NO. 24923 SAFAT, 13110 — SAFAT — KUWAIT, to arrive NO LATER THAN 31ST OCTOBER 1987.

# **Psychiatrists**

\$84,200-\$103,400 (contract) \$66,400-\$77,000 (classified) (salaries under review) (plus \$4,168 per year patient care allowance)

Challenging career opportunities now-exist with the MINISTRY OF HEALTH, Lakehead Psychiatric Hospital, a 237-bed accredited teaching facility affiliated with the University of Western Ontario. You will provide active treatment and educational/consultative services in the hospital and to the community. The ministry offers a \$40,000 income-tax-free underserviced area grant, paid quarterly over four years, and a general benefits package. Short-term and part-time contracts also available. The Ministry of Health has a smoke-free workplace policy. Location: Thunder Bay, a city of 125,000 which has excellent transportation services to Toronto, Winnipeg and Minneapolis, and year-round recreational facilities. The college and university provide a wide range of educational opportunities.

**Qualifications:** Speciality certificate in psychiatry from the Royal College of Physicians and Surgeons of Canada: licensed or eligible for licensing by the Ontario College of Physicians and Surgeons.

Please submit application/resume, quoting file HL-24-14/87, as soon as possible to: Dr. J. B. Frost, Medical Director, Lakehead Psychiatric Hospital, 580 Algoma Street North, P.O. Box 2930, Thunder Bay, Ontario, P7B 5G4.

**Equality of Opportunity for Employment** 



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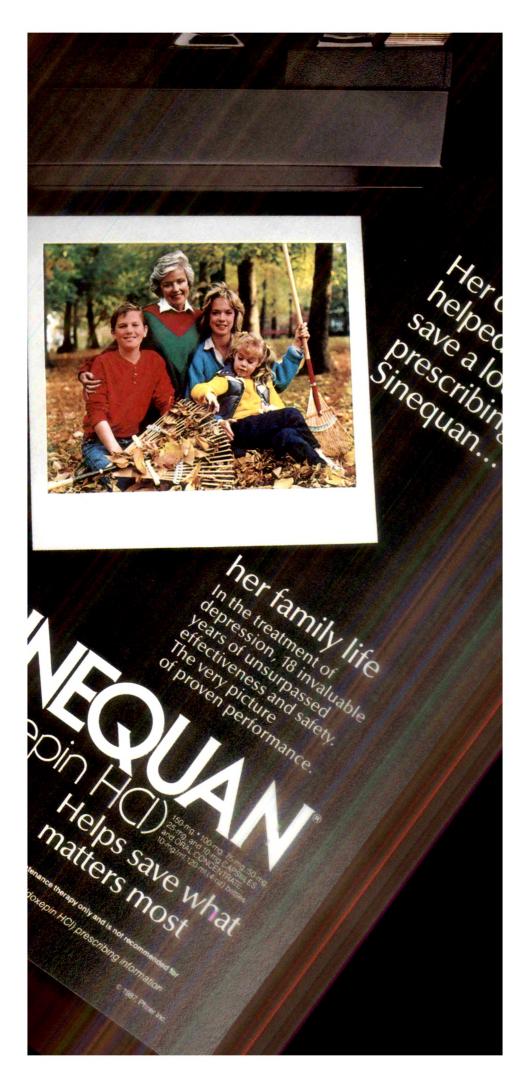
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# **APA ME**

Office of N AMERICAI 1400 K Str Washingto

# SUBSC

APA Circul AMERICAI 1400 K Str Washingto



- BRIEF SUMMARY
  SINEQUAN® (doxepin HCI) Capsules/Oral Concentrate
  Indications. SiNeQUAN is recommended for the treatment of:
  1. Psychoneurotic patients with depression and/or anxiety.
  2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol)
- 3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction hould be considered if the patient is receiving other drugs concomitantly).
   4. Psychotic depressive disorders with associated anxiety including involutional depression and
- manic-dépressive disorders.

manic-uspressive instruers.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, steep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient

Clinical experience has shown that SINEOUAN is safe and well tolerated even in the elderly patient Owing to lack of clinical experience in the pediatric population, SINEOUAN is not recommended for use in children under 12 years of age.

Contraindications. SINEOUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind. SINEOUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients. Warnings. The once-a-day dosage regimen of SINEOUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients recovering other medications with anti-industric effects.

patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects. Usage in Geriatrics: The use of SINEQUIAN on a once-a-day dosage regimen in genatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

the nursing infant.

\*\*Usage in Children:\* The use of SINEQUAN in children under 12 years of age is not recommended.\*\*

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established. 
MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious mitiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since sucide is an inherent risk in any depressed patient and may remain so until significant

Patients should also be cautioned that their response to alcohol may be potentiated.

Since sucide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Antichilepticatic Effects. Dry mouth burred vision constitation and unique retention have been

tricyclics, the reactions should be considered when prescribing SINEUUAN.

Anticholimagic Effects: Dry mouth, blurred vision, constipation, and unnary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, discorentation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and sezures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported nocasionally.

occasionally.

Altergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred 
Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of 
bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura. 
Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of 
breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of 
inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Disziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, 
alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN (doxepin HCI) administration should be borne in mind. 
These are not indicative of addiction and gradual withdrawal of medication should not cause these 
symptoms.

Inese are not indicative or addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day. In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 700 mg/day.

300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day. The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. His once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedrume. The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not Amin-analyge prince is apparent before the analogous sant teneur. Opining and be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth

Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyper-thermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.

2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.



# INDEX TO ADVERTISTERS

# **AUGUST 1987**

The publications of an advertisement in this journal does not imply endorsement of the proauct or service by th American Psychiatric Association.

BIO-LOGIC SYSTEMS CORPA
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DE;L AMO HOSPITALA1
DORSEY PHARMACEUTICALS  Mellaril
DUPONT PHARMACEUTICALS Symmetrel
EMPLOYMENT OPPORTUNITIESA28, A40–A <sup>2</sup>
McNEIL PHARMACEUTICALS Haldol
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MEETINGS AND CONFERENCESAl
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Ativan ......A9-A1

# For a Different Kind of Calm



Introducing
BuSpar
(buspirone HCl)

For Brief Summary, please see the last page of this advertisement

Mead Johnson
Pharmaceuticals
Introduces

# Buspirone HCl)

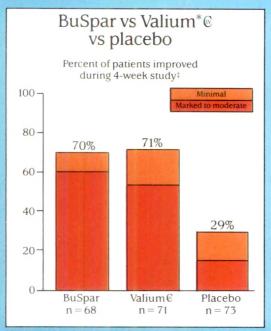
# A different kind of calm

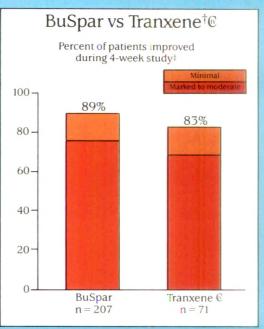
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.<sup>1,2,3</sup>

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.<sup>4,5</sup>

# Proven anxiolytic effectiveness over a 4-week course of therapy of





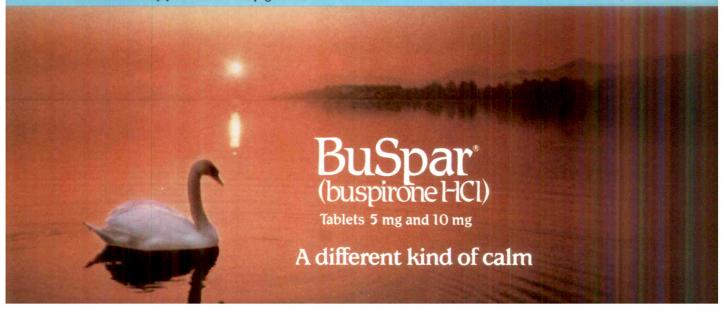
\*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.

‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,\* and cardiovascular and gastrointestinal complaints.

\*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.

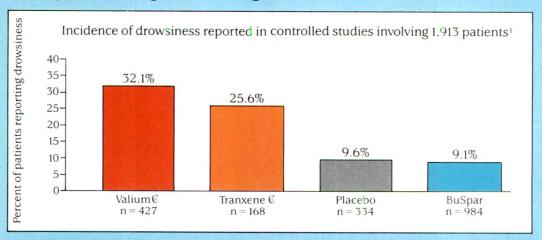


# Buspirone HCl)

# Anxiolytic efficacy without CNS-depressant activity

# Incidence of drowsiness no greater than placebo

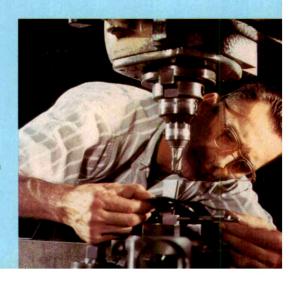
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.



# No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.<sup>2</sup>

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.



# No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.\*3



# No apparent abuse liability

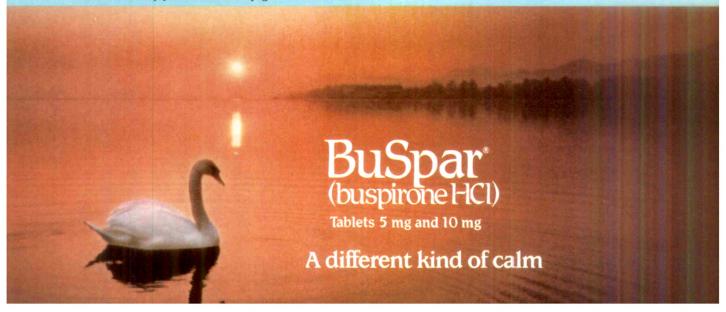
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.<sup>4,8</sup>

# Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

\*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



# Buspirone HCl)

# Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

# Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1



Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

# At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is not a controlled substance.

# Patient selection

BuSpar will <u>not</u> block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a benzodiazepine to BuSpar:

- 1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
- 2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

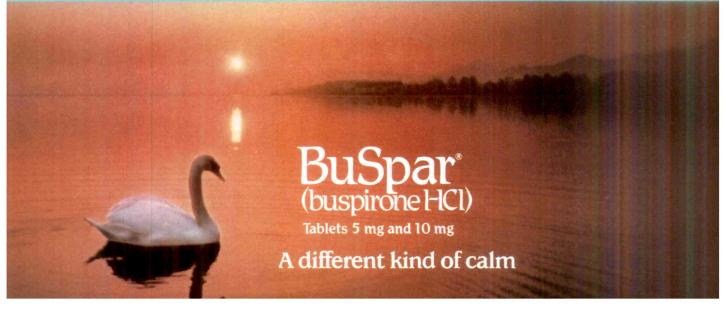
# BuSpar...the first choice in anxiolytic therapy when:

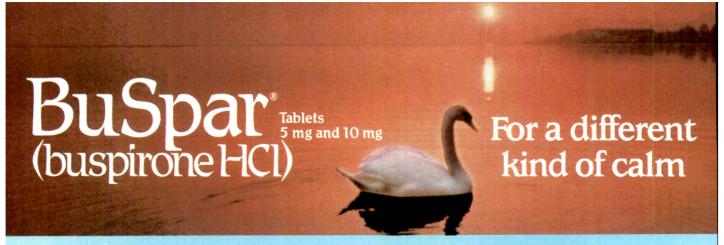
Treatment requires regular dosing for more than a few days

Patient functioning is key to safe and successful treatment

The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





# CONTRAINDICATIONS:

# WARNINGS:

The administration of BuSpar to a patient taking a menoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

# Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent

patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to with-draw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over vary-ing time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drugs use can be identified only after several years of marketing.

Information for Patients:

Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

# Drug Interactions:

Drug Interactions:

Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

# **Nursing Mothers:**

Administration to nursing women should be avoided if clinically possible. Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age

No unusual adverse age-related phenomena have been identified in elderly patients

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:

The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple com-

plaints, none of which could be characterized as primary,

plaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: Cardiovascular: tachycardia/palpitations 1%. CNS: dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. EENT: blurred vision 2%. Gastrointestinal: nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. Musculoskeletal: musculoskeletal: musculoskeletal: musculoskeletal: musculoskeletal: musculoskeletal aches/pains 1%. Neurological: numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. Skin: skin rash 1%. Miscellaneous: headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

tremor 1%. Skin: skin rash 1%. Miscellaneous: headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:

The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 17/100 patients; infrequent are those occurring in 17/00 to 17/100 patients; infrequent are those occurring in 17/00 to 17/100 patients; and rare are those occurring in less than 17/100 aptients; and rare are those occurring in less than 17/100 aptients; and rare are those occurring in less than 17/100 patients; and the patients of the state of the state

# DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Signs and Symptoms:

No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

# **Recommended Overdose Treatment:**

General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

# For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

- maceutical Division Representative.

  REFERENCES

  1. Newton RE, et al: A review of the side effect profile of buspirone. Amer J Med 1986;80(3B):17-21.

  2. Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. J Clin Psychiatry 1982;43 (12, Sec 2):45-55.

  3. Mattila MJ, et al: Acute effects of buspirone and alcohol on psychomotor skills. J Clin Psychiatry 1982;43 (12, Sec 2):56-60.

  4. Cole JO, et al: Assessment of the abuse liability of buspirone in recreational sedative users. J Clin Psychiatry 1982;43(12, Sec 2):69-74.

  5. Rickels K, et al: Buspirone, clorazepate and withdrawal. American Psychiatric Association, 138th Annual Meeting, Dallas, TX, May 18-24, 1985. Abstract No. NR74, pg 51.

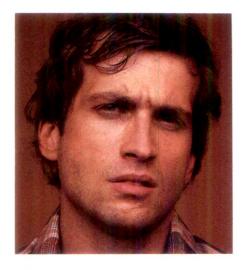
  6. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. J Clin Psychiatry 1982;43 (12, Sec 2):61-86.

  7. Cohn JB, et al: Double-blind comparison of buspirone and clorazepate in anxious outpatients. Amer J Med 1986;80 (3B):10-16.

  8. Griffith JD, et al: Investigation of the abuse liability of buspirone in alcohol-dependent patients. Amer J Med 1986;80 (3B):30-35.



PHARMACEUTICALS
Bristol-Myers U.S. Pharmaceutical
and Nutritional Group
Evansville, Indiana 47721 U S A



# For your schizophrenic patients

- Easily recognized color-coded tablets and tablet design
- Concentrate dropper calibrated in milligrams to facilitate dosage adjustment, as low as 1/2 mg.

# Make sure they receive HΔLD















# and not a substitute

The following is a brief summary only, Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate. 
HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any 
cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, 
dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the 
syndrome appears to be highest among the elderly, especially elderly women, it is impossible to refly upon 
prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop 
the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is 
unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are 
believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs 
streams treated to the scateral turcrasse. However, the syndrome can develon although much less commonly after. believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome many remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of freatment producing a satisfactory clinical response should be sought. The

harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. It signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

\*\*Usage in Pregnancy\*\* (see PRECAUTIONS - Usage in Pregnancy) \*\*Combined Use With Lithium\*\* (see PRECAUTIONS - Drug Interactions).

\*\*General\*\* Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of a figural pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoaquilants, since an isolated instance of interference occurred with the effects of one anticoaquilant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL. The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including pronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity. Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension. Drug Interactions: Patients receiving lithium plus haloperdol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay. Carcinogeneisty studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the usual daily human dose for chronic or resistant patients, there was a statistically significant increase in to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and

impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis. the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (halopendol) Decanoate are

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have

that compound a well as foll And Doc Decanoate.

See a reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses, Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. Tardive Dyskinesia. As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia but until original properties of the proper

confusion, vertigo, grand mal seizures, and exaceroation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholineric drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (riregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptom instability (riregular pulse discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes. Hematologic Effects: Reports of mid, usually transitieukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. Liver Effects: Tachycardia, hypotension, hypotension, blood of the properties and only in association with other medication. Liver Effects: Innaired liver function and/or jaundice. Dermatologic Reactions: Maculopapular and acneform reactions, isolated cases of photosensitivity, loss of hair. Endocrine Disorders: Lactation, breast engorgement, mastaligia, menstrual irregularities, gynecomasta, impotence, increased libido, hyperplycemia, hypoglycemia and hyponatremia. Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. Autonomic Reactions: Dry mouth, blurred vision, unrary retention, diaphoresis, and prapism. Respiratory. Effects: Laryngospasm, bronchospasm and increased depth of respiration. Special S





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Patient portrayed by professional model.

Please see brief summary of Prescribing Information on the preceding page.

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Emphasis added

<sup>1.</sup> Grinspoon L (ed): Care and treatment of schizoprenia—Part II, in The Harvard Medical School Mental Health Letter 1986; 3(1):1.

## THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 144, Number 9

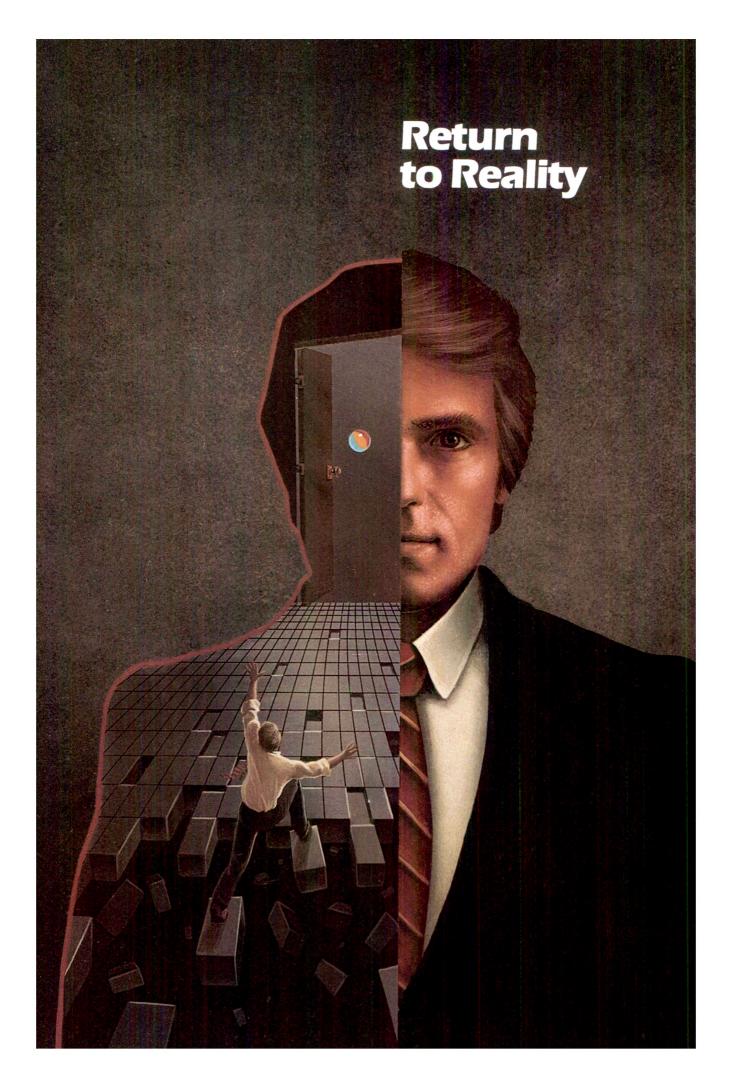
September 1987

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Alterations in Immunocompetence During Stress,
Bereavement, and Depression:
Focus on Neuroendocrine Regulation
By Joseph R. Calabrese, Mitchel A. Kling, and Philip W. Gold

Current Status and Future Directions of Research on the American Indian Child By Alayne Yates

Official Journal of the American Psychiatric Association



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- ☐ Apparently activates withdrawn, apathetic or detached patients
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'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics. However, when encountered, these symptoms are generally readily controlled.

Before prescribing, see complete prescribing information in SK&F Co. literature or <u>PDR</u>. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias, bone marrow depression, liver damage

liver damage

Warnings: Tardive dyskinesia [TD] may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic does increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppressigns and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Penodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symp-

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include. Hyperpyrexia, muscle nightly: altered mental status and evidence of autonomic instability.

The management of MMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy. 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems

"Stelazine" Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive [e.g., have had blood dyscrasias, jaundice] to any phenothiazine. Caution patients about activities requiring alertness [e.g., operating vehicles or machinery], especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and

potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

**Precautions:** Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular systems impaired since hypotension has occurred. Anternetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high dose may result in cumulative effects with severe C. N. S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with diauroma.

Patients with a history of long-term therapy with "Stelazine" and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat

cautiously in persons who will be expósed to extreme heat Phenothiazines may diminish the effect of oral anticoagulants Phenothiazines and diminish the effect of oral anticoagulants Phenothiazines are produce alpha-adenering blockade. Concominant use of phenothiazines with proprianolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothrazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoni toxicity, dosage adjustments of anticonvulsants may be necessary if neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuna (PKU) test results Adverse Reactions: Drowsiness, dizziness isking to the condition of the co

Other adverse reactions reported with Stelazine [trifluoperazine HCI, SK&F] or other phenothiazines: S. T. T. St. College of the stellar in sufficiency of pheochromocytoma]

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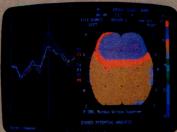
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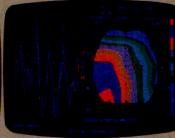
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P-300 of patient with Morbus Wilson Syndrome



FFT of EEG (EC), Morbus Wilson Syndrome



P-300 of patient with Alzheimer's Disease

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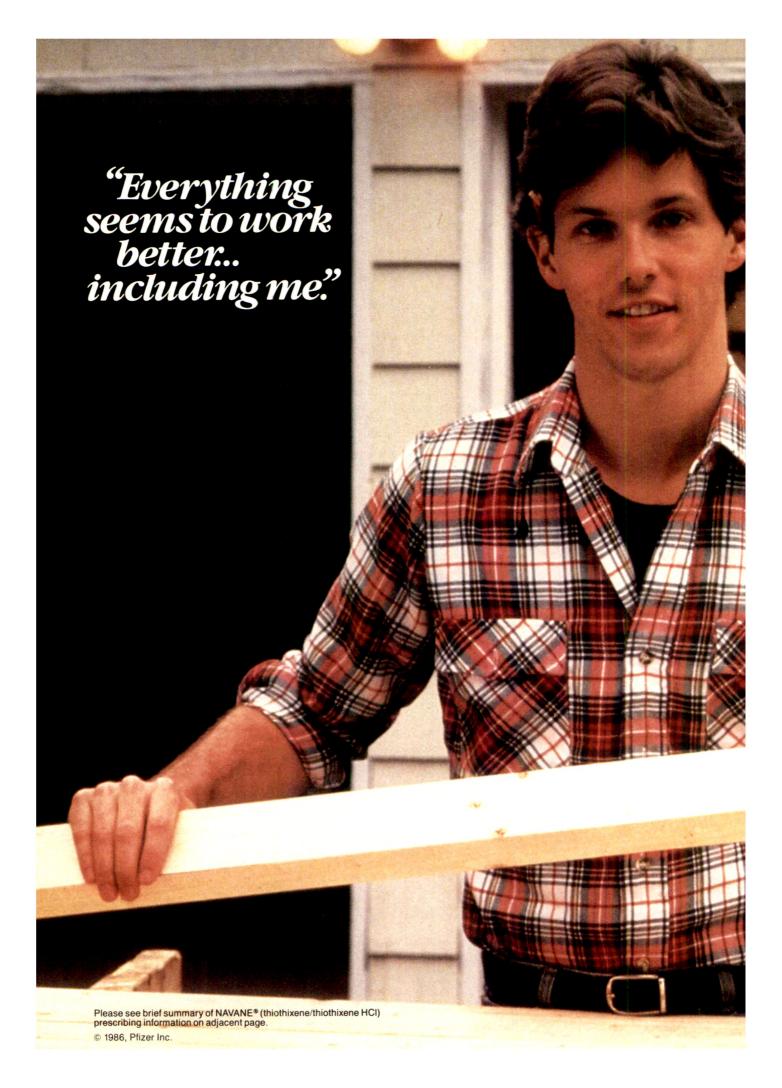
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References: 1 Bressler B. Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. **2** DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. **3** DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4 Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*, Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. **5** Dillenkofter RL, Gallant DM, George RB, et al. Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. 6 Data available on request from Roerig.

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Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg (thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity

between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered. **Warnings:** Tardive Dyskinesia—Tardive dyskinesia, a syndrome consisting of potentially irreversible untary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may sup-press (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that. 1) is known to respond to neuroleptic drugs, and. 2) for whom alternative equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should

be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refe the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the per-formance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first

few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible

additive effects (which may include hypotension) with CNS depressants and with alcohol. **Precautions:** An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions

such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with

other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, bil-iary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association be-tween chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered

tween current entitled animistration in these drugs and maininary funioringenesis, the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then

only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothix ene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane

Cardiovascular effects: Tachycard a, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pres-sure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene) These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs. In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some pa-tients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue,

appear to be interestable. The syndrome is characterized by hyphilms and involvements of the original face, mouth or jaw (e.g., protrusion of tongue, putting of cheeks, puckering of mouth, chewing movements.) Sometimes these may be accompanied by involuntary movements of extremities

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)
Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been in-

frequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated vagranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Altergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been re-ported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane II persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia,

hypoglycemia, hyperglycemia, and glycosuria
Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine

derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute be-havior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recom-

mendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily, If indicated, an increase to 60 mg/day total daily dose is often

effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma. Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric layage is helpful. For

Navane oral and Inframuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include ampheta-tine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be freated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phe-

nothiazine intoxication.



## For a Different Kind of Calm



Introducing
BuSpar
(buspirone HCl)

Mead Johnson Pharmaceuticals Introduces

# Buspirone HCl)

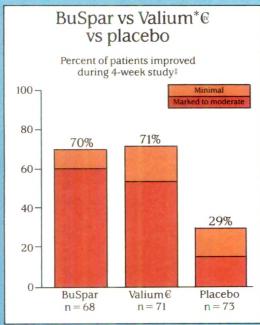
## A different kind of calm

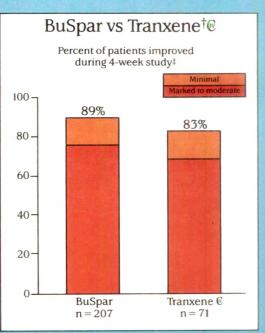
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.<sup>1,2,3</sup>

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.<sup>4,5</sup>

## Proven anxiolytic effectiveness over a 4-week course of therapy "





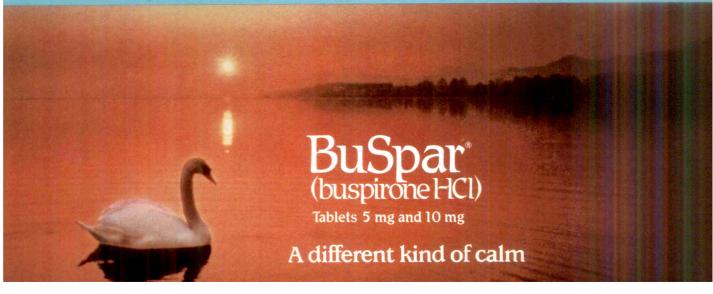
\*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate

‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,\* and cardiovascular and gastrointestinal complaints.

\*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.

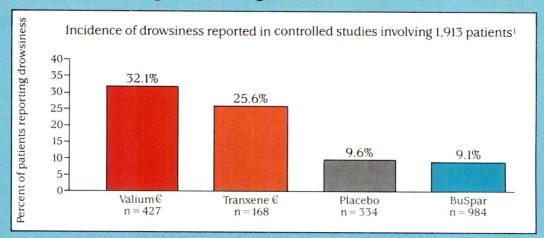


# Buspirone HCl)

## Anxiolytic efficacy without CNS-depressant activity

## Incidence of drowsiness no greater than placebo

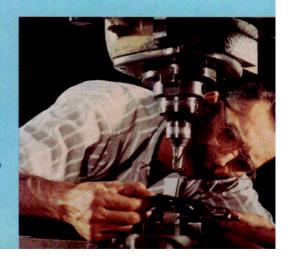
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.'



## No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.<sup>2</sup>

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.



## No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.\*3



## No apparent abuse liability

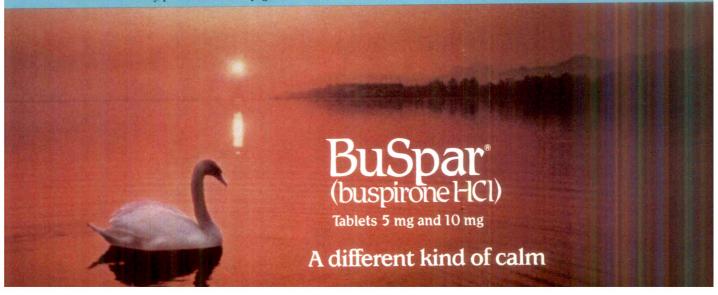
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.<sup>4,8</sup>

## Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

\*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



# Buspirone HCl)

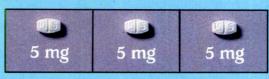
## Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

## Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1



**Dosage adjustment**—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

## At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is not a controlled substance.

## Patient selection

BuSpar will <u>not</u> block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

## If you elect to switch a patient from a benzodiazepine to BuSpar:

- 1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
- 2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

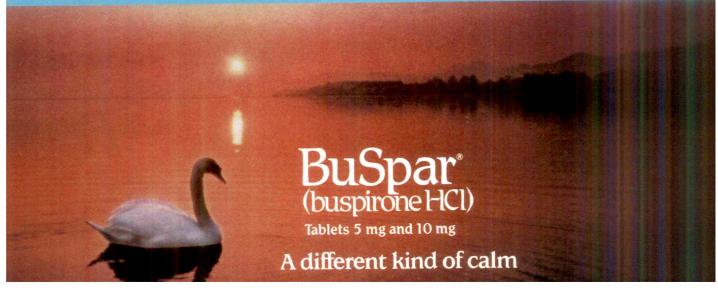
## BuSpar...the first choice in anxiolytic therapy when:

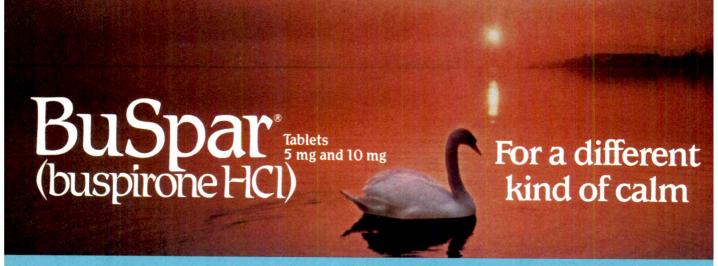
Treatment requires regular dosing for more than a few days

Patient functioning is key to safe and successful treatment

The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





## CONTRAINDICATIONS:

## WARNINGS:

The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

## Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:

Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:

Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:

Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyret\* (trazodone) and BuSpar may have caused 3 - to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers: Administration to nursing women should be avoided if clinically possible

## Pediatric Use: The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly: No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, head-ache, nervousness, light-headedness and excitement.

## Associated with Discontinuation of Treatment: The more common events causing discontinuation

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple com-

plaints, none of which could be characterized as primary

## Incidence in Controlled Clinical Trials:

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: Cardiovascular: tachycardia/palpitations 1%. CNS: dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. EENT: blurred vision 2%. Gastrointestinal: nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. Musculoskeletal: musculoskeletal aches/pains 1%. Neurological: numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. Skin: skin rash 1%. Miscellaneous: headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

## Other Events Observed During the Entire Pre-Marketing Evaluation:

Other Events Observed During the Entire Pre-Marketing Evaluation:

The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. Cardiovascular: Frequent was nonspecific chest pair; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. Central Nervous System: Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. EENT: Frequent were finantius, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered state, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. Endocrine: Rare were galactorrhea and thyroid abnormality. Gastrointestinal: Infrequent were flattleince, ancrexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. Genitourinary: Infrequent were unrary frequency. urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. Musculoskelevalitic infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. Neurological: Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. Respiratory: Infrequent were hy

## **DRUG ABUSE AND DEPENDENCE:**

Controlled Substance Class: BuSpar is not a controlled substance

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

- REFERENCES
   Newton RE, et al: A review of the side effect profile of buspirone. Amer J Med 1986;80(38):17-21.
   Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. J Clin Psychiatry 1982;43 (12, Sec 2):45-55.
   Mattila MJ, et al: Acute effects of buspirone and alcohol on psychomotor skills. J Clin Psychiatry 1982;43 (12, Sec 2): 55-80.
   Cole JO, et al: Assessment of the abuse liability of buspirone in recreational sedative users. J Clin Psychiatry 1982;43(12, Sec 2): 69-74.
   Rickels K, et al: Buspirone, chorazepate and withdrawal. American Psychiatric Association, 138th Annual Meeting, Dallas, TX, May 18-24, 1985. Abstract No. NR74, pg 51.
   Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. J Clin Psychiatry 1982;43 (12, Sec 2):81-86.
   Cohn JB, et al: Double-blind comparison of buspirone and clorazepate in anxious outpatients. Amer J Med 1986;80 (3B):10-16.
   Griffith JD, et al: Investigation of the abuse liability of buspirone in alcohol-dependent patients. Amer J Med 1986;80 (3B):30-35.

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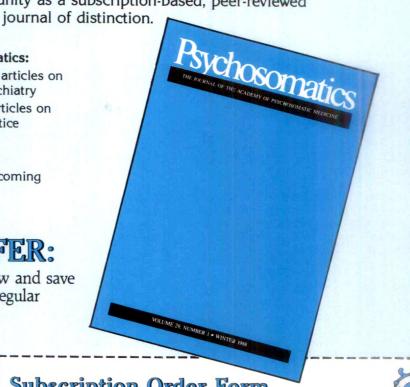
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## **NOVEMBER**

November 1–5, International Congress on Suicide, Universidade Federal do Estado de Rio de Janeiro, Rio de Janeiro. Contact Luis Vasquez, M.D., MILA, 38760 Northwood Dr., Wadsworth, IL 60083; 312-249-1900, 800-367-7378.

November 2–5, annual meeting, American College of Emergency Physicians, San Francisco. Contact Collin C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-659-0911.

November 5–7, 11th National Conference on Correctional Health Care, National Commission on Correctional Health Care and American Correctional Health Services Assoc., Chicago. Contact NCCHC, 2000 North Racine, Suite 3500, Chicago, IL 60614; 312-528-0818.

November 6-7, The Many Faces of Late-Life Depression, Boston Society for Gerontologic Psychiatry, Boston. Contact Sandra White, BSGP, 64 Hancock Ave., Newton, MA 02159; 617-527-5550.

November 6–9, annual meeting, National Rehabilitation Assoc., New Orleans. Contact David L. Mills, Executive Director, 633 S. Washington St., Alexandria, VA 22314; 703-836-0850.

November 7–12, annual meeting, Association of American Medical Colleges, Chicago. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, D.C. 20036; 202-828-0400.

November 8–13, annual meeting, Association of Military Surgeons of the United States, Las Vegas. Contact Lt. General Max B. Bralliar, Executive Director, P.O. Box 104, Kensington, MD 20895; 301-933-2801.

November 10–13, annual meeting, Association for Medical Education and Research in Substance Abuse, Rockville, Md. Contact AMERSA Conference Coordinator, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912; 401-863-1109.

November 11–15, annual meeting, American Academy of Medical Administrators, Las Vegas. Contact Thomas R. O'Donovan, Ph.D., President, Congress Bldg., Suite 525, 30555 Southfield Rd., Southfield, MI 48076; 313-540-4310.

November 12–13, 10th MSIS National Users Group Patient Tracking Conference, Suffern, N.Y. Contact Shelley Sprung,

Conference Coordinator, Information Sciences Division, Nathan S. Kline Institute, Orangeburg, NY 10962; 914-359-0002.

November 12–15, Assembly of District Branches, American Psychiatric Association, Washington, D.C.

November 15–17, part II examinations, American Board of Psychiatry and Neurology, New York. Contact Stephen C. Scheiber, M.D., Executive Secretary, American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

November 16–17, annual meeting, Council of Medical Specialty Societies, Chicago. Contact Richard S. Wilbur, M.D., Executive Vice-President, P.O. Box 70, Lake Forest, IL 60045; 312-295-3456.

November 16–17, 6th Annual Conference on Prescription Drug Information and Education, National Council on Patient Information and Education, Washington, D.C. Contact NCPIE, 1625 I St., N.W., Suite 1010, Washington, DC 20006; 202-466-6711.

November 16–18, annual conference, National Council on Family Relations, Atlanta. Contact Cynthia Winter, Conference Coordinator, NCFR, 1910 West County Road B, Suite 147, Roseville, MN 55113; 612-633-6933.

November 16–20, International Conference on the Rehabilitation of the Brain Injured Person—A Neuropsychological Perspective, Tel-Aviv, Israel. Contact The Secretariat, P.O.B. 50006, Tel-Aviv 61500, Israel; 03-654571; Telex 341171 KENS IL.

November 16–21, annual meeting, Society for Neuroscience, New Orleans. Contact Nancy Beang, Executive Secretary, 11 Dupont Circle, N.W., Suite 130, Washington, DC 20036; 202-462-6688.

November 18–22, annual meeting, American Anthropological Assoc., Chicago. Contact Edward J. Lahman, Executive Director, 1703 New Hampshire Ave., N.W., Washington, DC 20009; 202-232-8800.

November 19–21, annual conference, The Common Boundary, Washington, D.C. Contact Ann Simpkinson, Conference Director, Common Boundary, 7005 Florida St., Chevy Chase, MD 20815; 301-652-9495.





The active metabolite of amitriptyline

## All the efficacy of amitriptyline and a favorable side effect profile

Because of anticholinergic activity, PAMELOR (nortriptyline HCI) should be used with caution in patients who have glaucoma or a history of urinary retention.

Contraindications: 1) Concurrent use with a monoamine oxidase MAO) inhibitor, since hyperpyretic crises, severe convulsions, and atalities have occurred when similar tricyclic antidepressants were ised in such combinations. MAO inhibitors should be discontinued or at least two weeks before treatment with Pametor\* (nortriptyline ICI) is started. 2) Hypersensitivity to Pametor (nortriptyline HCI). ross-sensitivity with other dibenzazepines is a possibility 3) The icute recovery period after myocardial infarction **Narnings**: Give only under close supervision to patients with car-

liovascular disease, because of the tendency of the drug to produce inus tachycardia and to prolong conduction time, myocardial infarcion, arrhythmia, and strokes have occurred. The antihypertensive iction of quanethidine and similar agents may be blocked. Because of Is anticholinergic activity, nortriptyline should be used with great aution in patients who have glaucoma or a history of urinary reten-ion. Patients with a history of seizures should be followed closely, ince nortriptyline is known to lower the convulsive threshold. Great are is required in hyperthyroid patients or those receiving thyroid nedication, since cardiac arrhythmias may develop. Nortriptyline nay impair the mental and/or physical abilities required for the per-ormance of hazardous tasks, such as operating machinery or driving car, therefore, the patient should be warned accordingly Excessive consumption of alcohol may have a potentiating effect, which may ead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation

Vise in Pregnancy — Sale use during pregnancy and lactation has not seen established, therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be veighed against the possible hazards

Use in Children - Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been

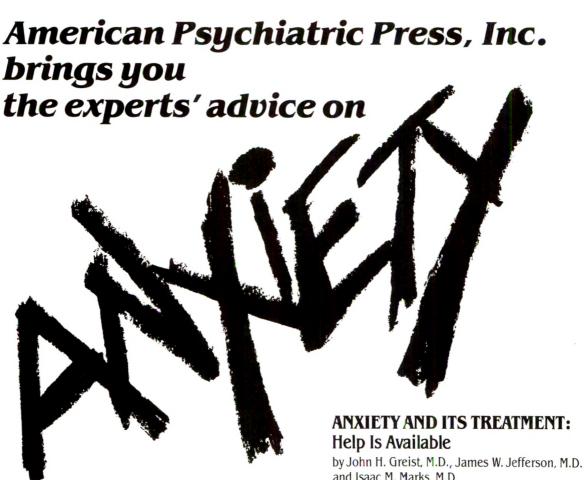
Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symp toms, in overactive or agitated patients, increased anxiety and agitation may occur, in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a fricyclic antidepressant has been shown to produce a "stimu-lating" effect in some depressed patients. Troublesome patient hostility may be aroused Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment, in this regard. it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels

Adverse Reactions: Cardiovascular Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke *Psycriatric* Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, panic, nightmares, hypomania, exacerbation of psychosis. *Neurologic*. Numbness, tingling, pares

thesias of extremities, incoordination, ataxia tremors, peripheral neuropathy, extrapyramidal symptoms, seizures, alteration in EEG patterns tinnitus Anticholinergic Dry mouth and rarely, association ated sublingual adenitis, blurred vision, disturbance of accommoda tion, mydriasis, constipation, paralytic ileus urinary retention delaved micturition, dilation of the urinary tract. Ailergic Skin rash delayed micturition, dilation of the urinary tract. Allergic petechiae, urticaria, itching, photosensitization (avoid excessive ex petechiae, urticaria, itching, photosensilization (avoid excessive exposure to sunt ght), edema (general or of face and tongue), drug lever cross-sensitivity, with other tricyclic drugs. Hematologic. Bonemarrow depression, including agranulocytosis eosinophilia purpura, thrombocytopenia. Gastrointestinal. Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatilis, abdominal cramps, black-tongue. Endocrine. Gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, testicular swelling, elevation or depression of thord sugar levels, syndrome of inanorporate. ADH. (antision of blood sugar levels, syndrome of mappropriate ADH (anti-diuretic hormone) secretion. *Other*. Jaundice (simulating obstructive), altered liver function, weight gain or loss, perspiration. flushing, urinary frequency, nocturia, drowsiness, dizziness, weak-ness, fatigue, headache, parotid swelling, alopecia, Withdrawal Symptoms—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known, general supportive measures are indicated, with gastric lavage.





and Isaac M. Marks, M.D.

For people being treated for anxiety, people considering treatment for anxiety, people wondering whether their anxiety needs treatment, and families and friends of anxiety patients. It is a guide to understanding anxiety, what it is and how it is treated.

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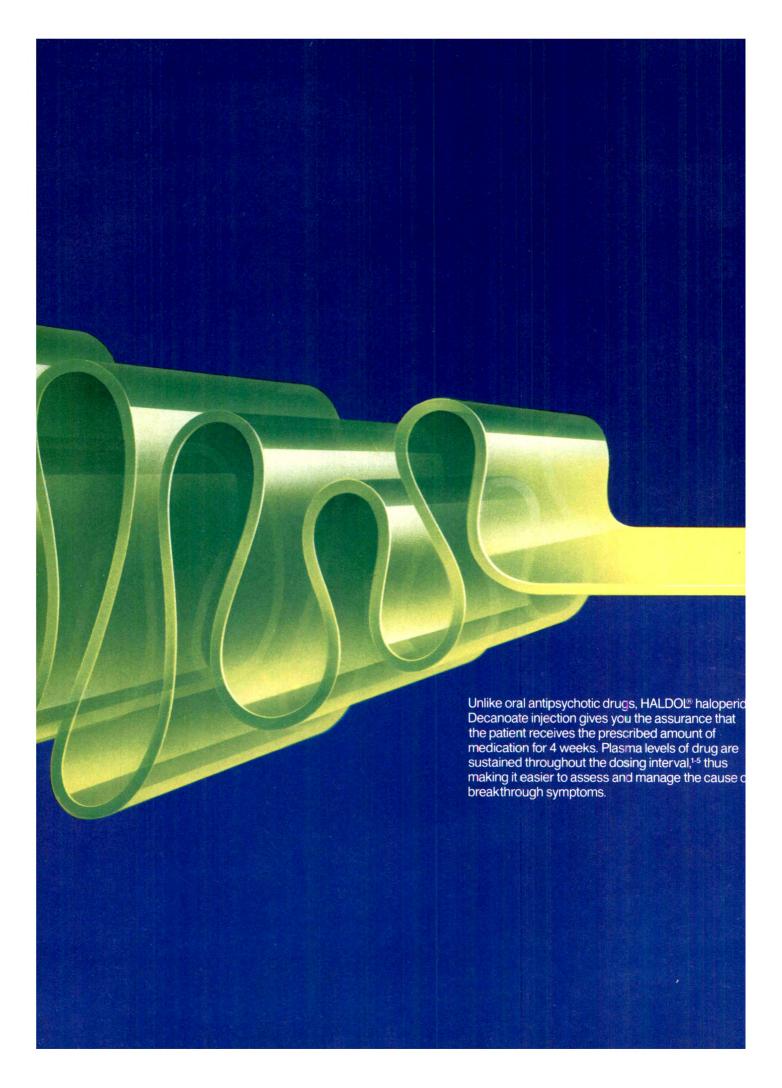








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# Sustained drug levels with a single monthly dose

## HALDOL DECANOATE (HALOPERIDOL) INJECTION

the therapeutic constant in schizophrenia

## Pharmacokinetic profile facilitates monthly dosing

Smooth, steady drug delivery has been shown to achieve efficacy equal to oral HALDOL, but at lower monthly doses. 1 The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about 3 weeks.6

The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy have, at some time, been treated with, and have tolerated well, short-acting HALDOL in order to exclude the possibility of unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

## Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

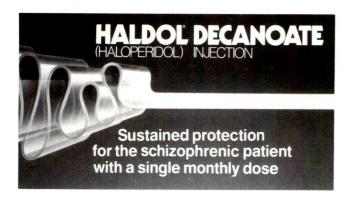
- References

  1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial
  comparing intramuscular haloperidol decanoate and oral haloperidol
  in chronic schizophrenic patients: Efficacy, safety, and dosage
  equivalence. J Clin Psychopharmacol 1986;6(No. 1, Suppl);30S-37S.
   Reyntjens AJM, Heykants JJP, Woestenborghs RJH, et al:
  Pharmacokinetics of haloperidol decanoate. Int Pharmacopsychiatry
  1982;17:238-246.
- Deberdt R, Elens P, Berghmans W, et al: Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. An open multicenter study. Acta Psychiatr Scand 1980;62:356-363.
- Kissling W, Möller HJ, Walter K, et al: Double-blind comparison of haloperidol decanoate and fluphenazine decanoate. Effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. *Pharmacopsychiatry* 1985;18:240-245.

   Roose K: Haloperidol decanoate as a replacement for maintenance.
- Noose N. Haopentool decandate as a repractner from maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. *Acta Psychiatr Belg* 1982;82:216-223.
   Nayak RK, Doose DR, Nair NPV. The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients (Submitted for publication).

Please see brief summary of prescribing information on next page





The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL becanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require treatment despite the pre

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) Combined Use With Lithium: (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperiol. See PRECAUTIONS. Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances. Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EE6 abnormalities, because HALDOL may lower the convulsive threshold if indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulants, since an isolated instance of interference occurred with the office of the are discontinued simultaneously, carrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsyc

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in hose who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving

those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension. 

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. 
As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol. 
Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay. 
Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). 
In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antiosvchotic drugs elevate prolactin levels: the elevation persists during chronic administra-

noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in nammary neoplasms has been found in rodents after chronic administration of antisychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Nursing Mothers: Infants should not be nursed during drug treatment. 
Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted. 
Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decancate are those of HALDOL. Serious values experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decancate. As with all injectable medications, local tissue reactions have been reported with HALDOL. Decancate. 
CNS Effects: Extrapyramidal Reactions—Neuronoscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment Generally they involved Parkinson-like symptoms which when first observed were usually mild on moderately severe and usually reversible. Other types of neuronuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyriscrises) have been reported far less frequently, but were often more severe. Severe extrapyramidas by the been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-nated since they occur at relatively low doses. Generally, extrapyramidal reactions have been exported at relatively low doses. Generally, extrapyramidal reactions have been exported at relatively low doses. Generally severe when the observation and the drug may have to be discontinued in such cases. Withdrawal Energent Neurological Signs—Abrupt discontinuation or short-term antipsychotic therapy is generally uneventful. However, and the drug may have to be discontinued in such cases (Withdrawal Energent Neurological Signs—Abrupt discontinuation or short-term antipsychotic therapy is generally uneventful. However, and the drug may have to be discontinued in such cases these are indistinguishable from "Tartive Dyskinesia" except for duration, it is unknown the first produced in the superior of the superior of the superior of the superior of the superior o

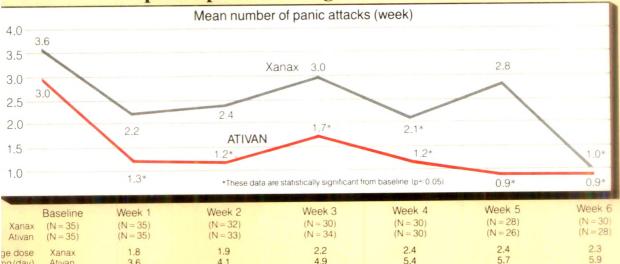
IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing informa-

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic trients with moderately severe to very severe symptoms.

6/3/87



## Ativan® vs Xanax®† (alprazolam) in reduction of panic episodes during six-week study



ng/day)

Ativan

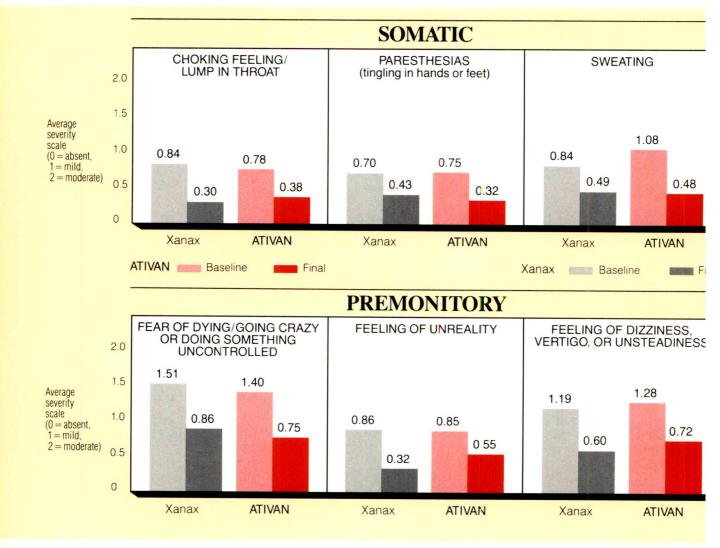
Helps keep panic attacks under control

\*As defined in Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised). Used by permission of the American Psychiatric Association. †Xanax is a registered trademark of The Upjohn Company.

See last page for brief summary of prescribing information.

## Ativan<sup>®</sup> (lorazepam) effectively reduc

A multicenter, double-blind, six-week study compared Ativan\* (N = 40) to Xanax (N = 37) in relieving symptoms of panic disorder as defined by DSM-III-R diagnostic criteria<sup>1,2</sup>



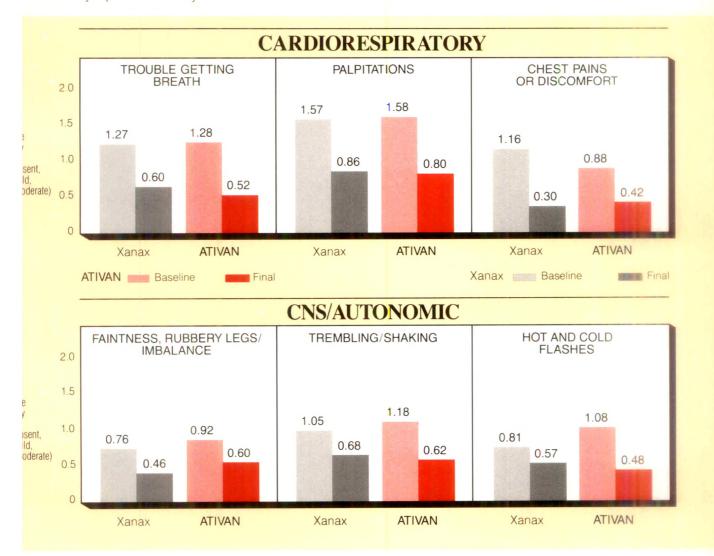
The panic attacks usually last minusinitially, are unexpected, i.e., they do no situation that almost always causes an attacks are not triggered by situations

## **CUDY CONFIRMS:**

## ajor symptoms of panic attacks

## Efficacy equal to Xanax in reducing the symptoms of panic attacks1

As compared to Xanax, Ativan\* demonstrated equivalent reduction in individual symptom severity<sup>1</sup>



more rarely, hours. The attacks, at least immediately beautiful and some source of the control o

Helps keep panic attacks under control

## For relief of anxiety Prescribe Ativan®

## Because:

Simple metabolism by conjugation, no active metabolites

Clearance is not significantly delayed by age, liver, or kidney dysfunction

Little likelihood of drug interactions with numerous, commonly prescribed medications

(All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)



## Specify Ativan®-maintain the integrity of your prescription while assuring your patients' therapy

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Dispense as written
- Brand necessary
- May not substitute
- Medically necessary
- No substitutions
- NDPS (no drug product selection)

References: 1. Data on file. Wyeth Laboratories. 2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, ed 3 (revised). Washington. DC Diagnostic and Statistical Marida of mo American Psychiatric Association, 1987

## Brief Summary of Prescribing Information.

**Indications and Usage:** Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle

Warnings: Not recommended in primary depressive disorders or psychoses.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants. Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for

Precautions: In depression accompanying anxiety, consider possibility for suicide. For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated; anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at flow/floy/day (about 6 times maxihent. Esophageal dilation occurred in rats treated with iorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbilurates

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drugtreated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of concentral malformations associated with use of migra transpillings (chloridate). Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiaze-poxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its plucuronide. lorazepam and its glucuronide

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3.500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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The Gospel According to Woman: Christianity's Creation of the Sex War in the West (1986), by Karen Armstrong. Garden City, N.Y., Anchor Press (Doubleday & Co.), 1987, 352 pp., \$17.95.

Communication and Cognition in Normal Aging and Dementia, by Kathryn A. Bayles, Ph.D., and Alfred W. Kaszniak, Ph.D., with the assistance of Cheryl K. Tomoeda, M.S. Boston, College-Hill (Little, Brown and Co.), 1987, 368 pp., \$29.50.

How to Persuade Your Lover to Use a Condom . . . and Why You Should, by Patti Breitman, Kim Knutson, and Paul Reed. Rocklin, Calif., Prima Publishing and Communications, 1987, 81 pp.,

\$4.95 (paper).

The Elderly Uncooperative Patient (1986), edited by T. L. Brink.

New York, Haworth Press, 1987, 188 pp., \$24.95. Dual Disorders: Counseling Clients With Chemical Dependency and Mental Illness, by Dennis C. Daley, M.S.W., Howard Moss, M.D., and Frances Campbell, M.S.N. Center City, Minn., Hazelden, 1987, 141 pp., no price listed (paper).

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The Fantasy Bond: Effects of Psychological Defenses on Interpersonal Relations (1985), by Robert W. Firestone, Ph.D., in collaboration with Joyce Catlett, M.A. New York, Human Sciences

Press, 1987, 397 pp., \$14.95 (paper).

Mental Health and the Environment, edited by Hugh Freeman, M.Sc., M.A., B.M., B.Ch., F.R.C. Psych., D.P.M. New York,

Churchill Livingstone, 1984, 469 pp., \$69.00.

The Letters of Sigmund Freud and Arnold Zweig (1970), edited by Ernst L. Freud; translated by Elaine and William Robson-Scott. New York, New York University Press (Columbia University Press, distributor), 1987, 184 pp., \$30.00; \$15.00 (paper).

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Reality Orientation for the Elderly, 3rd ed., by Sylvester Kohut, Jr.. Ph.D., Jeraldine J. Kohut, R.N., M.A. N.H.A., and Joseph J Fleishman, Ph.D. Oradell, N.J., Medical Economics, 1987, 146 pp., \$8.95 (paper).

The Voices of Robby Wilde, by Elizabeth Kytle. Washington, D.C..

Seven Locks Press, 1987, 329 pp., \$17.95.

Handbook of Schizophrenia, vol. 1: The Neurology of Schizophre nia, edited by Henry A. Nasrallah and Daniel R. Weinberger Henry A. Nasrallah, editor-in-chief. New York, Esevier, 1986 406 pp., \$92.50.

Advice for Life: A Woman's Guide to AIDS Risks and Prevention. A National Women's Health Network Guide, by Chris Norwood.

New York, Pantheon, 1987, 172 pp., \$5.95 (paper).

Occupational Therapy in Mental Health: A Guide to Outcomes Research, edited by Patricia C. Ostrow and Kathy L. Kaplan Rockville, Md., American Occupational Therapy Association 1987, 339 pp., \$32.50 (paper).

The Heart of History: Individuality in Evolution, by John Wei-Perry. Albany, State University of New York Press. 1987, 238 pp.,

\$39.50; \$12.95 (paper).

Dementia, edited by Brice Pitt, M.D., F.R.C. Psych. New York. Churchill Livingstone (White Plains, N.Y., Longman, distributor) 1987, 335 pp., \$75.00.

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ers, 1987, 358 pp., \$16.95 (paper).

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1987, 181 pp., \$21.50; \$11.95 (paper).

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Press, 1987, 287 pp., \$39.95.

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BRIEF SUMMARY SINEQUAN® (doxepin HCI) Capsules/Oral Concentrate

- Indications. SINEQUAN is recommended for the treatment of:

  1. Psychoneurotic patients with depression and/or anxiety.

  2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with
- 3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).

  4. Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

pprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient.

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Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind. SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with antichniencie effect.

patients taking with reductations with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has no been established. There are no data with respect to the secretion of the drug in human milk and its effect on

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended

because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

\*\*Usage with Alcohol:\*\* It should be borne in mind that alcohol ingestion may increase the danger.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen. 
Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the

tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures. Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported

cocasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Costolicational: Nausea vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aph-

Done marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura. Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomasta in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms should be borne in mind.

These are not indicative of addiction, and cradual withdrawal of medication should be to me in mind.

These are not indicative of addiction and gradual withdrawal of medication should not cause these

symptoms. 
Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day. In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

Journal of the state of the sease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day. The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. The 150 mg capsule strength is intended for maintenance therapy only and is not second and the initiation at leastness. recommended for initiation of treatment

recommended for initiation of treatment.

Anti-anxite prefect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.

2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyper-

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.

2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine is rapidly metabolized, the dosage should be repeated as required. salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convolisions may respond to standard anticonvolsant therapy, however, barbiturates may potentiate any respiratory depression. Diaysis and forced divinesis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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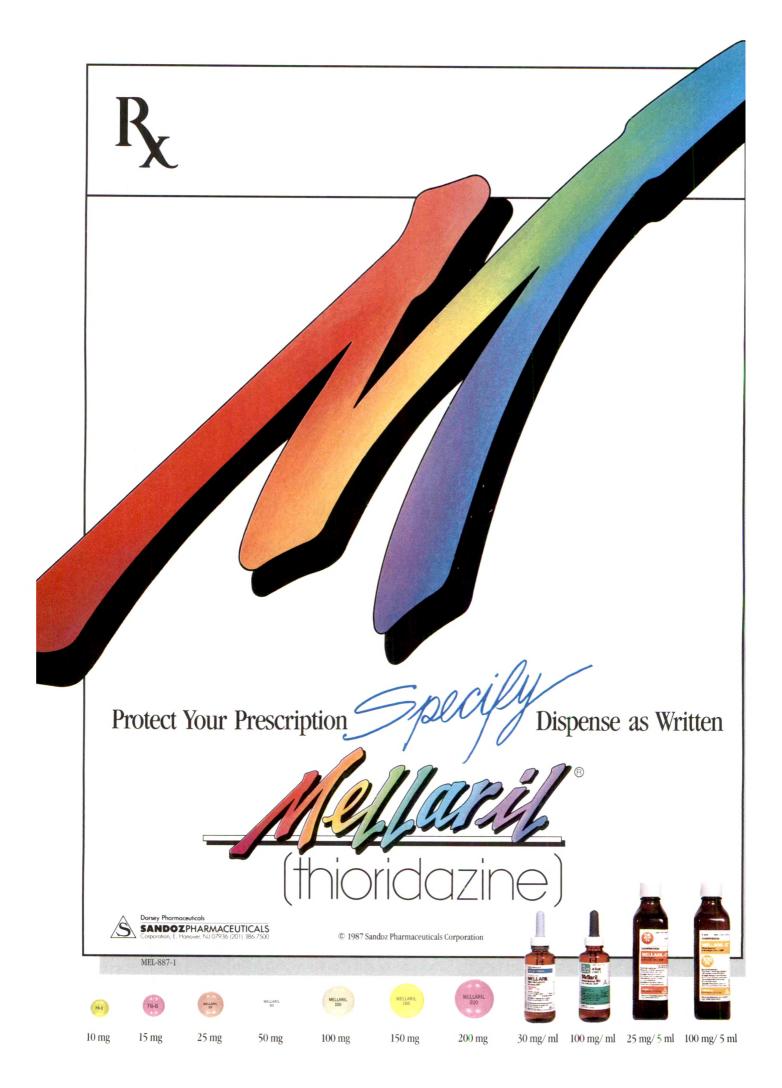
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# THE AMERICAN JOURNAL OF PSYCHIATRY

# Alterations in Immunocompetence During Stress, Bereavement, and Depression: Focus on Neuroendocrine Regulation

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There is now clear evidence that stress, bereavement, and depression can compromise specific components of the immunologic apparatus. The first part of this paper gives an overview of fundamental immunology and is followed by a review of the patterns, possible causes, and potential clinical implications of abnormal immunoregulation. After a discussion of the immunomodulating properties of glucocorticoids, the authors conclude with an overview of the many factors that mediate the complex interdependence between immunologic function, the brain, and neuroendocrine regulation. (Am J Psychiatry 1987; 144:1123–1134)

The last decade has produced a series of studies which indicate that psychological stress and psychiatric illness can compromise immunologic function. Hence, these studies suggest that psychological state may influence susceptibility to illness and/or its course and prognosis. In addition, a growing body of evidence suggests that the humoral concomitants of the immune response can gain access to and affect CNS function and, possibly, behaviors that might be adaptive during illness. The mechanisms by which psychological state influences immunologic function have not been defi-

nitely elucidated, although several have been suggested. In this paper, we begin with a brief overview of the structure and components of the immunologic system and then give a more detailed description of the actual function and interrelationship of these components. This overview is provided in an attempt to place in context the growing body of data that link psychological functioning and immunologic reactivity.

#### OVERVIEW OF THE IMMUNOLOGIC APPARATUS

A major function of the immune system is to distinguish "self" from "nonself" with extraordinary specificity. This capacity must occur in the context of an ability to respond to invasion by foreign antigens without disrupting central homeostatic mechanisms. Accomplishing this task has required the evolution of an exceptionally complex system of cellular and humoral components. Classically, immunologists have subdivided the immunologic apparatus into systems subserving cellular (1) and humoral immunity (2). Cellular immunity is now believed to be principally mediated by lymphocytes acting directly on an invading antigen, while humoral immunity is thought to be rendered by lymphocytes which produce antibodies that circulate systemically (3). Other immunologic functions are ascribed to phagocytic cells, such as neutrophils, monocytes, macrophages, and the complement system. Over the last 10 years, the boundaries between humoral and cellular subdivisions of the immune response have become less distinct as each component has been shown to be intimately dependent on the other. More recently, complex and crucial interactions between lymphocytes and phagocytic cells have also been elucidated in great detail.

The organs of the immune system that respond to

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Helper Helper T cell T cell (CD4+) lymphocyte (CD4+) Granulocyte Thymus Lymphoid Nonlymphoid Suppressor Suppressor stem cell stem cell T cell T cell (CD8+) (CD8+) 0 lymphocyte marrow lymphocyte Macrophage Monocyte Lymph node Bone marrow (bursal equivalent?) Plasma PHAGOCYTIC LYMPHOCYTIC SERIES SFRIFS IgG, IgM, IgA, IgD, IgE

FIGURE 1. Ontogeny of Immunocytes, Showing Differentiation of Precursor Cells Into Immunocompetent Cells

antigenic challenge are called lymphoid organs and include the bone marrow, thymus, lymph nodes, spleen, tonsils, appendix, and clumps of lymphoid tissue in the small intestines known as Peyer's patches. The primary lymphoid organ is the bone marrow, which produces stem cells for both the lymphoid and nonlymphoid (phagocytic) immunocytes (figure 1).

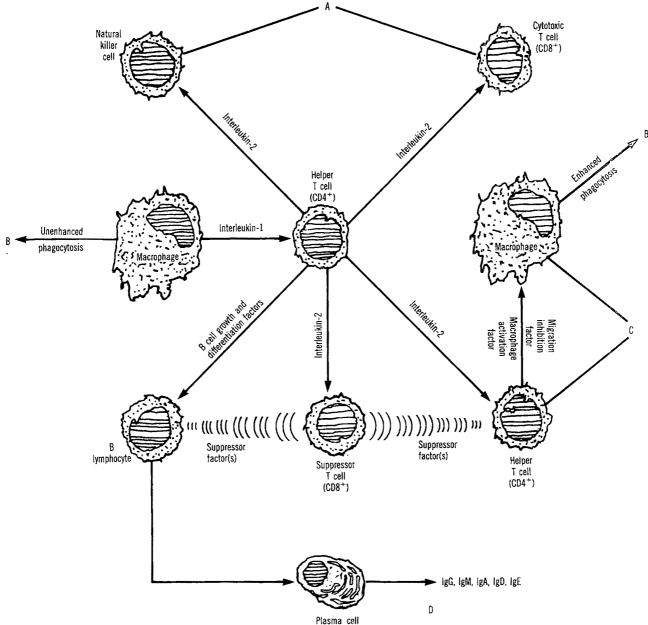
Lymphoid stem cells give rise to two major subdivisions of lymphocytes, depending on which lymphoid organ serves as the site in which they mature. The cells of one major subdivision, the T lymphocytes, mature in the thymus (4), where they differentiate under the control of a group of soluble mediators called thymosins into at least two major functional subsets (helper T cells and suppressor T cells) (5). The T lymphocytes mediate what had classically been termed cell-mediated immunity (1). Lymphoid stem cells that mature in the bone marrow are called B lymphocytes (6); their designation as B lymphocytes reflects the fact that early studies done in avian species showed that analogous cells mature in the bursa of Fabricius (7), a structure with no known analogy in humans. Nonlymphoid stem cells mature in various loci, including the bone marrow, the systemic circulation, and various tissue sites; those which mature in bone marrow and the systemic circulation are called monocytes and granulocytes. Monocytes further differentiate into macrophages when they become fixed in tissues (figure 1).

Immunologic Functions Mediated by B Lymphocytes

The activation of B lymphocytes results in their growth and differentiation into two cell lineages. One of these transformations results in mature antibody-secreting plasma cells; this differentiation, which occurs under the control of helper T cell-secreted "B cell differentiation factor," illustrates the interdependence between B and T lymphocyte systems (8) (figure 2). Some activated B cells, however, do not undergo plasma cell differentiation; instead, they turn into resting, nondividing cells called memory B cells, which upon a second exposure to the same antigen rapidly differentiate into antigen-specific plasma cells. All of the antibodies generated from a given clone of B cell-dependent plasma cells have identical molecular structure (9).

Classically, immunologic functions mediated by B lymphocytes (humoral or antibody-mediated immunity) have been thought to confer protection against encapsulated bacteria, to neutralize toxins produced by bacteria, to prevent viral reinfection, and to carry out immediate allergic reactions, such as anaphylaxis and asthma (10). Typically, antibodies are unable to penetrate cells, so intracellular bacteria and viruses are not susceptible to their effects (11). Although antibody-mediated immunity has not been thought to play a primary role in conferring protection against intra-

FIGURE 2. Cellular and Humoral Components of Immunity<sup>a</sup>



<sup>a</sup>A=foreign tissues (i.e., transplants, tumor cells, viruses (intra- and extracellular); B=all exogenous antigens (i.e., bacteria, viruses, particulate matter), dead self-components; C=delayed hypersensitivity (i.e., fungi, mycobacterium tuberculosis, other granuloma-producing agents); D=bacteria, toxins, allergens (immediate hypersensitivity), viruses (only extracellular).

cellular viruses and fungal agents or in tumor cell surveillance, it plays an adjunctive role in the immune processes directed against these foreign antigens (11).

Plasma cells produce five classes of antibodies, or immunoglobulins (Ig): IgG, IgM, IgA, IgE, and IgD. These classes differ in structure, in their sites of origin, and, in some instances, in their mode of conferring immunocompetence (12). For instance, IgG, the major circulating antibody, enters most tissue spaces and functions by coating microorganisms, a process called

opsonization (12). This makes it possible for polymorphonuclear neutrophils and macrophages to recognize, engulf, and destroy foreign antigens such as bacteria. IgM is confined to the vascular compartment, usually assuming star-shaped pentameric clusters, and is capable of directly annihilating bacteria. Both IgG and IgM can activate the first component of the classical complement pathway. This system is composed of about 20 circulating proteins (13). Activation of the first component leads to sequential activation of a cascade

of 20 proteins, which ultimately promote direct lysis of microorganisms. Some of the components of the system facilitate phagocytosis through the opsonization of foreign antigens, while other components mediate chemotaxis, a process by which circulating phagocytes are attracted to sites of infection. Still other components are involved in the release of histamine during acute anaphylaxis.

IgA concentrates in body fluids like tears, saliva, and secretions of the respiratory and gastrointestinal tracts, functioning to protect these mucosal entrances to the body. Although their mechanisms of action are unknown, they are thought to act as a barrier, denying microorganisms access to mucosa rather than being involved in direct killing (14). IgE attaches itself to foreign antigens (allergens) and then to the surface of specialized tissue cells known as basophils and mast cells (15). This causes mast cells and basophils to release such intracellular amines as histamine, slowreacting substance of anaphylaxis, and prostaglandins of the E series; these substances and others mediate acute hypersensitivity (15). Little is known about IgD, which is present on B cell surfaces and is thought to facilitate the process of lymphocyte activation by an unknown mechanism.

# Immunologic Functions Mediated by T Lymphocytes

T lymphocytes have been classically distinguished from B lymphocytes on the basis of where they mature and the manner in which sheep red blood cells aggregate around them in vitro, forming a rosette pattern (16). Moreover, in contrast to B cells, which confer immunity indirectly by humoral secretion (i.e., antibodies), T cells confer immunity directly by cellantigen interaction (cell-mediated immunity). It has been recently learned, however, that T cells also produce humoral mediators of immunity known as lymphokines (interferon, interleukin-2, B cell differentiation factor, etc.). Independent of B cells and their antibody products, T cells confer protection against viral and fungal infections, reject grafts of foreign tissue, cause delayed hypersensitivity reactions, and fight tumor growth.

On the basis of the presence of cell surface antigens measured by monoclonal antibody techniques, two major subsets of T lymphocytes were initially identified: helper and suppressor T lymphocytes (figure 2). The names "helper" and "suppressor" refer to their roles in both antibody synthesis and delayed hypersensitivity (the latter being the in vivo manifestation of cellular immunity that leads to tissue injury, e.g., granulomatous disease). Helper T lymphocytes are designated CD4+ (17) and, with the exception of providing the effector cells for delayed hypersensitivity, confer their immunologic effects by helping macrophages and other T or B lymphocytes. For instance, helper T cells produce lymphokines called B cell growth and differentiation factors, which promote the differentiation of B cells into plasma cells, and the

secretion of antibody (8) (figure 2). They also produce another lymphokine called interleukin-2 (previously known as T cell growth factor), which assists in the development of cytotoxic T and suppressor T cells (18). Because helper cells perform many important functions, it is not surprising that a disease as lethal as acquired immune deficiency syndrome (AIDS) represents a specific defect in helper T cell function (19). For this reason, ongoing therapeutic trials for AIDS are evaluating the potential benefit of administration of interleukin-2, a helper T cell-secreted lymphokine.

Suppressor T cells are designated CD8+ (17) and, by less well understood "suppressor factor(s)," are believed to block the differentiation of B cells into plasma cells and the activity of helper T cells in delayed hypersensitivity (20). In so doing, they "turn off" antibody-mediated immunity, serving as important counterregulatory immune modulators; hence, defective autoantigen-specific suppressor T cell function has been implicated in the pathophysiology of autoimmune disease (21).

A proper balance between help and suppression appears necessary for the regulation of antibody synthesis and the control of delayed hypersensitivity. Although suppressor T cells do not have cytotoxic properties, a second major subset of T lymphocytes, cytotoxic T cells (also designated CD8+), exists and does have direct killing potential (22). Cytotoxic T cells constitute the effector cells that respond to specific antigens to confer antiviral, antitumor protection and to mediate the transplant rejection phenomena (23); they are the targets of immunosuppressive agents used after transplant surgery. As expected, patients receiving immunosuppressive therapy have an increased incidence of de novo malignancies, particularly skin cancers and Epstein-Barr virus-induced lymphomas (24).

Recently, a subpopulation of non-B, non-T lymphoid cells has been identified. These naturally occurring cells appear as large, granular lymphocytes and constitute about 5% of peripheral white blood cells, many appearing as atypical lymphocytes seen in peripheral smear. Other names for these cells are null cells (non-T, non-B) and natural killer cells (25). Like cytotoxic T cells, natural killer cells attack and destroy tumor cells and virus-infected cells. However, in contrast to cytotoxic T cells, whose function requires recognition of specific viral or tumor antigens, natural killer cells can attack tumor cells and virus-infected cells directly, without prior antigen interaction. This direct cytotoxic property is believed to be in part mediated by natural killer cell secretion of the lymphokine interferon (26). For this reason, interferon has been administered in clinical trials to patients with various malignancies (27).

# Other White Blood Cells Involved in Cell-Mediated Immunity

In addition to the lymphocytes we have described, other cells not in the lymphocyte series play important

roles in cell-mediated immunity. These cells are phagocytic in nature and are subdivided into two categories based on morphology: polymorphonuclear and mononuclear phagocytes. Polymorphonuclear phagocytes are circulating cells that recognize, ingest, and destroy foreign antigens. Polymorphonuclear neutrophils, eosinophils, and basophils are examples of these cells; they are also called granulocytes, because they contain granules filled with potent enzymes that enable them to digest microorganisms and contribute to inflammatory and allergic reactions (28).

Mononuclear phagocytes constitute the reticuloendothelial system and are composed of monocytes and macrophages. Macrophages have at least three important functions. The first of these is to kill pathogens after either unenhanced or enhanced phagocytosis. The second is to recognize, process, and present antigens to helper T cells (29). Macrophages accomplish this task by ingesting the antigens and then incorporating the antigenic determinants of the pathogen into the structure of their own cell surface for presentation to helper T cells (29). Macrophages accomplish their third immunologic function by assisting in T lymphocyte activation through their secretion of interleukin-l, a lymphokine also known as T cell activating factor or lymphocyte activating factor (30) (figure 2). Mononuclear phagocytes that circulate are called monocytes. These cells are derived from monoblasts and promonocytes in the bone marrow and become macrophages when they become fixed or immobilized outside the vascular space.

### Mounting an Immune Response

The immune response calls into play a series of complex redundant mechanisms that work together to protect against invading pathogens. In this section, we review a typical sequence of immunologic events that unfold when the immune system is challenged by a foreign antigen.

Defense starts at the body surface. Such defenses include barriers presented by the skin and mucous membranes and various forms of mechanical maneuvers (e.g., sneezing or "sweeping" by respiratory cilia). In addition, there is the local production of such antimicrobial factors as oral-nasal lysozymes and gastric acidity. The immunologic apparatus plays a relatively small role in the efforts to prevent pathogens from penetrating the host's external barriers. However, IgA, which is found in mucous secretions throughout the nasopharynx and gastrointestinal tract, is believed to be a relevant component of the body's efforts to prevent penetration of its external shield (14).

Once a pathogen penetrates the host's external barriers, the body will attempt to eliminate it by unenhanced phagocytosis (figure 2). If this process is successful, the pathogen is eliminated and symptoms of disease are not seen. If it is unsuccessful, a variety of concerted antigen-specific humoral and cellular immu-

nologic mechanisms are called into play. For this to take place, there must first be recognition of the antigen by macrophages located within the reticuloendothelial system (29). The antigen is processed by the macrophage in such a way that a portion of the antigenic determinants of the pathogen is displayed on the surface of the macrophage along with its own self-determinants, i.e., human leukocyte antigens (29). The macrophage then presents these antigenic determinants to each of the subsets of T cells (helper, suppresssor, and cytotoxic T cells). Shortly after this takes place, the macrophage secretes interleukin-1 (figure 2) (30). This lymphokine activates those T cells which have learned to recognize the antigenic determinants of the pathogen. Were it not for self-determinants on the macrophage cell surface, lymphocytes would be unable to proceed with activation, as recognition of both self and nonself is a prerequisite for T cell activation. The subset of helper T cells then secretes interleukin-2, T cell growth factor, which promotes the proliferation of specific clones of activated CD4<sup>+</sup> (helper) and CD8<sup>+</sup> (suppressor and cytotoxic) T cells (18).

The subset of activated helper T cells goes on to produce a variety of other lymphokines to augment the immune response. Some of these lymphokines enhance humoral (antibody-mediated) immunity, and some enhance cell-mediated immunity. Simplistically, B cell growth factor causes B cell proliferation, and B cell differentiation factor causes the antigenic clones of B cells to mature in antibody-producing plasma cells (figure 2) (19). These plasma cell-secreted antibodies then either directly lyse extracellular pathogens or indirectly assist in cellular immunity by a variety of mechanisms; for instance, antibodies can enhance phagocytosis by coating the pathogen's cell surface (opsonization).

Another lymphokine, called migration inhibition factor, inhibits the random migration of macrophages through tissues, resulting in the accumulation of macrophages around the area of T cell activation (31). Macrophage activation factor, now known also as y-interferon, enhances the direct cytolytic activity of those macrophages located around the site of invasion (32). These helper cell-secreted lymphokines serve to amplify the small number of lymphocytes originally recruited to recognize and destroy the invading pathogen. They enhance the functional activity of reticuloendothelial cells (i.e., macrophages) and promote the specialization of B cells. The subset of activated suppressor T cells then secretes suppressor factor(s) that "turn off" the immune response when the host has successfully defended itself against the invading pathogen (figure 2). These circulating lymphokines may gain access to the central nervous system and potentially exert effects on central neuromodulators that are thought to influence neuroendocrine function and behavior. Thus, these lymphokines may play a unique integrative role, allowing the immune response to an invading pathogen to promote adaptive endocrine and behavioral responses that have potential survival value.

# Genetic Control of the Human Immune Response

The human immune response is mounted under the regulation of immune response (Ir) genes located on the short arm of chromosome 6 (33). These genes, along with other genes that specify "self" antigens, comprise the human leukocyte antigen (HLA) complex, also known as the major histocompatibility complex (34). The complex is present on every cell in the body and determines histocompatibility by directing the synthesis of cell surface markers, which identify a given cell as a natural part of the body. Hence, the HLA complex enables immune cells to distinguish self from nonself. Certain HLAs are associated with specific diseases, i.e., ankylosing spondylitis, type I diabetes mellitus, Graves' disease, myasthenia gravis, and, possibly, depressive disorder (33–36). Typically, these diseases are of unknown cause, are segregated in families, and are associated with immunologic abnormalities (33, 34).

# IMPACT OF STRESS, BEREAVEMENT, AND DEPRESSION ON IMMUNOLOGIC FUNCTION

Clinical Studies of the Impact of Bereavement and Other Stressors

In 1977 Bartrop et al. first reported a relationship between psychological state and immunologic function (37). The subjects who participated in that study were 26 men and women whose spouses were seriously ill. Each subject provided a blood sample 1-3 weeks and 6 weeks after the death of his or her spouse; a group of 26 age- and sex-matched control subjects provided similarly spaced blood samples. Bartrop et al. first studied mitogen stimulation, one of the most widely applied in vitro probes of immunologic function in subsequent studies of stressed, bereaved, and depressed subjects. To perform these studies, Bartrop et al. isolated lymphocytes from the blood of each subject and cultured them with substances known to stimulate lymphocyte proliferation. These substances, derived from the extracts of plant seeds, are called mitogens because of their ability to stimulate mitosis. Two mitogens known to preferentially stimulate T lymphocytes were selected: phytohemagglutinin (PHA) and concanavalin A. It was noted that T lymphocyte responses to low doses of PHA were reduced both at 3 weeks and at 6 weeks after the death of the spouses, during which time active bereavement occurred.

At higher doses of both mitogens, T lymphocyte responses in bereaved subjects were significantly lower at 6 weeks than at the first sampling, suggesting a cumulative, time-dependent effect of stress. At the time Bartrop et al. made their finding, several of the important mechanisms of T cell proliferation had not yet

been elucidated, so these researchers could not point to possible mechanisms of the blunted T cell response to mitogen stimulation in bereaved subjects. A review of figure 2 shows that many factors could be involved, including abnormalities in interleukin-1 and interleukin-2 secretion or actions and deficient recognition of the antigenic determinants of the mitogen as foreign.

Functionally, potential defects in T cell activity such as Bartrop et al. described could compromise many important immune mechanisms, including resistance to viral and fungal agents and impairment of the integrity of tumor cell surveillance. In addition, since T cells also contribute to B cell proliferation by secreting B cell differentiation factors, functional defects in T cell activity could also affect humoral-mediated immunity (e.g., bacterial infections, anaphylaxis).

In addition to in vitro stimulation with a potent nonspecific T cell stimulus, Bartrop et al. assessed in vivo T lymphocyte function by challenging this system with several specific antigens known to produce a characteristic delayed hypersensitivity reaction that is apparent on routine skin testing. In contrast to their abnormal responses to mitogen stimulation, the bereaved subjects responded normally at all times to the skin testing procedures. This indicates that a wide variety of cellular interactions required for delayed hypersensitivity (interleukin-1, interleukin-2, macrophage activating factor, etc.) were largely intact (see figure 2). It should be noted, however, that anergy on skin testing implies a more profound compromise of the immunologic apparatus than abnormal responses to mitogen stimulation.

Bartrop et al. also measured a variety of basal indicators of immunologic function in their bereaved subjects, including T and B cell percentages and serum immunoglobulin concentrations. They also examined the serum protein electrophoretic pattern and screened for several autoantibodies, including rheumatoid factor, antinuclear factor, mitochondrial antibodies, and smooth muscle antibodies. Examination of all of these parameters yielded no abnormality.

Since Bartrop and associates' subjects did not receive standardized psychiatric evaluations or mood ratings, one cannot conclude that their data definitively support a relationship between the psychological stress of normal bereavement and immunocompromise. Their subjects could have suffered from major depression.

In another landmark study (38), Schleifer et al. prospectively assessed white blood cell count, T and B lymphocyte subpopulations, and mitogen stimulation of lymphocytes in culture in 15 men before and serially after the deaths of their wives from metastatic breast cancer. Although total white blood cell counts and T and B subpopulations were noted to be unchanged after bereavement, Schleifer et al. replicated Bartrop and associates' finding of blunted mitogen stimulation of lymphocytes in the bereaved population, this time doing so with three mitogens. The third mitogen Schleifer et al. used, pokeweed mitogen, is thought to be a T cell-dependent B cell mitogen. This raises the

possibility of impaired antibody formation in bereavement as well. Schleifer and his colleagues noted suggestive, but not definitive, evidence of spontaneous reversal of this finding on follow-up 4–14 months later. In this study also, bereaved subjects did not systematically receive standardized psychiatric diagnoses and mood ratings, again making it difficult to determine whether the reported immunocompromise was due to the stress of normal bereavement or some other occult psychiatric disorder, such as major depression.

In a third study that examined immunocompetence during bereavement, Linn et al. (39) studied various measures of humoral and cell-mediated immunity while carefully evaluating severity of depressive symptoms with the Hopkins Symptom Checklist. In vitro lymphocyte responses to PHA were significantly reduced only in bereaved subjects with high scores on the depression subscale of the rating instrument. Immunologic function was also shown to be reduced in this depressed subgroup of bereaved individuals when the assessment was based on the responses of their lymphocytes to incubation with allogeneic lymphocytes (i.e., lymphocytes taken from another individual), an in vitro procedure known as mixed lymphocyte cultures. This abnormality further suggests an alteration in one or more components of cell-mediated immunity, such as reduced interleukin-2 (figure 2). Lymphocyte responses to other antigens, concanavalin A, and pokeweed mitogen did not differ in the depressed and nondepressed subjects. Moreover, quantitative analyses of IgG, IgA, and IgM, in vivo responses to three delayed-hypersensitivity skin tests, and neutrophilic chemotaxis were also normal in all of the bereaved subjects. Although the authors could not account for the fact that abnormal lymphocyte responses were seen with mixed lymphocyte cultures and some, but not all, of the mitogens used for stimulation, they concluded that abnormalities, when noted, were confined to the subjects with demonstrable depressive symptoms.

To determine whether loneliness and stressful life events are associated with alterations in immunocompetence in patients with various psychiatric disorders, Kiecolt-Glaser et al. (40) assessed lymphocyte responses to PHA and pokeweed mitogen activity by incubating the patients' lymphocytes with radiolabeled tumor cells. They reported that a subgroup of patients with high scores on the UCLA Loneliness Scale showed the confluence of hypercortisolism (assessed only by spot checks of urinary cortisol), reduced lymphocyte responses to PHA (but not to pokeweed mitogen), and decreased natural killer cell activity. Abnormality in the latter suggests the possibility of compromised responsiveness to tumor, viral, and allogeneic (i.e., transplanted tissue) antigens in hypercortisolemic individuals. Deviations in natural killer cell activity and lymphocyte responses to PHA suggested that cellmediated immunity was preferentially impaired.

In a follow-up study (41), Kiecolt-Glaser et al. assessed immunocompetence in medical students stud-

ied 1 month before and during final examinations. In contrast to their previous study, which showed that loneliness per se rather than stressful life events compromised immune function, they noted that examination stress was capable of reducing natural killer cell activity. In this study, decrements in natural killer cell activity correlated with the degree of loneliness. Although much confusion exists in this area, studies which evaluate the immunomodulating potential of the different psychosocial stressors usually conclude that such qualitative changes as reduced lymphocyte responses to either mitogens or allogeneic cells are commonly seen (37-44). On the other hand, quantitative studies that have assessed numbers of the different white blood cells have not yielded conclusive findings (37, 38, 42). Quantitative assessment of immunoglobulin levels has likewise yielded conflicting data (37, 41, 44, 45).

It should be noted that although we have alluded to the theoretical implications of the aforementioned abnormalities during pyschosocial stress, there have been only retrospective studies of bereaved and chronically stressed individuals to assess their vulnerability to disease. At present, there can be no firm conclusion concerning the clinical implications of blunted lymphocyte responses to mitogenic or allogeneic stimulation. These responses merely suggest that in an artificial, in vitro situation, lymphocytes are less capable of undergoing mitoses, a finding that need not translate into clinically relevant immunocompromise. Studies that have assessed vulnerability to disease have been epidemiological rather than biochemical and convey a sense, though not definitive, that psychological factors can influence an individual's capacity to fend off disease. For example, Meyer and Haggerty (46) showed that chronic stress was related to increases in streptococcal infection in 16 families. Kasl et al. (47) showed that military cadets who experienced greater academic pressure were more likely than others to contract infectious mononucleosis. Baker and Brewerton (48) reported an increased incidence of stressful life events in the months preceding the onset of acute rheumatoid arthritis. Likewise, in a comprehensive review, Sklar and Anisman (49) cited a substantial literature to support the idea that cancer growth may be significantly augmented by stress and a sense of helplessness.

Extreme physical stress also diminishes immunocompetence, especially with regard to functions related to cell-mediated immunity. For instance, several studies have noted quantitative changes such as decreased T cell number and percentage and qualitative changes such as diminished lymphocyte responsivity to mitogenic and allogeneic stimulation. The effects of a variety of biological stressors on various components of immunologic function are summarized in table 1. These observations not only have intrinsic importance but also strongly suggest that a variety of physical, pharmacological, and biological variables should be controlled for in studies assessing immunocompetence.

**TABLE 1. Common Immunologic Findings During Stress** 

Study	Stressor	Cellular Immunity	Humoral Immunity		
Clot et al. (50)	Advanced age	Decreased number of T lymphocytes; decreased number of monocytes	Decreased number of B lymphocytes		
Kishimoto et al. (51)	Advanced age	Decreased lymphocyte responses to PHA <sup>a</sup> and concanavalin A; decreased lymphocyte responses to allogeneic cells (mixed lymphocyte cultures)	Normal lymphocyte responses to pokeweed mitogen		
Palmblad et al. (52)	Auditory stimula- tion during sleep deprivation	Increased lymphocyte synthesis of interferon; decreased neutro- phil and monocyte phagocytosis during sleep deprivation, but increased afterward	· ·		
Palmblad et al. (53)	Sleep deprivation	Decreased lymphocyte responses to PHA			
Eskola et al. (54)	Marathon run- ning	Decreased lymphocyte responses to PHA, concanavalin A, and purified protein derivative; increased WBC and neutrophil count; increased plasma cortisol			
Bistrian et al. (55)	Protein calorie malnutrition	Anergy with delayed-hypersensitivity skin testing; decreased number of lymphocytes			
Chandra (56)	Protein calorie malnutrition	Decreased lymphocyte responses to allogeneic cells; increased plasma cortisol; decreased number of T lymphocytes and helper cells; decreased serum thymic hormone			
Beisel et al. (57)	Single nutrient deficiencies (vita- mins, minerals, amino acids)	Decreased lymphocyte responses to mitogen stimulation; decreased number of T lymphocytes	Decreased antibody re- sponse to antigenic chal- lenge; decreased number of B lymphocytes		
Miller et al. (58)	Heavy cigarette smoking	Increased WBC and number of suppressor cells; decreased number of total lymphocytes; decreased helper-to-suppressor cell ratio			
Watson et al. (59)	Heavy alcohol use	Anergy with delayed-hypersensitivity skin testing; decreased lymphocyte responses to PHA and concanavalin A; increased number of helper cells; decreased number of suppressor cells			
Lazzarin et al. (60)	Opiate addiction	Anergy with delayed-hypersensitivity skin testing	Increased IgG and IgM		

<sup>&</sup>lt;sup>a</sup>PHA=phytohemagglutinin.

# Clinical Studies of the Impact of Affective Illness

Kronfol et al. (61) first examined immune function in depression. In this elegant study, 26 drug-free depressed subjects manifested blunted responses to mitogen stimulation with concanavalin A, PHA, and pokeweed mitogen. Schleifer et al. (62) replicated this finding in severely depressed patients and, in addition, presented the first data on abnormal lymphocyte subpopulations. They reported that absolute T and B lymphocyte cell counts were reduced, although the relative percentages were unchanged. In a subsequent study, Schleifer et al. (45) noted that mildly depressed outpatients showed normal immune parameters, compatible with an early study by Sengar et al. (63), which noted similar findings in euthymic patients with affective disorder. Recently, Calabrese et al. (64) also replicated Kronfol and colleagues' findings; in addition they documented elevated plasma levels of prostaglandin E1 and E2. These substances may directly account for deficits of cellular immunity through their counterregulatory immune-modulating properties (65). Alternatively, they could indirectly mediate immunocompromise by stimulating the hypothalamic-pituitaryadrenal (HPA) axis (66).

However, the findings of abnormal cellular immunity in drug-free affective illness were questioned when Albrecht et al. (67) were unable to replicate Kronfol et al.'s original findings in a group of 32 moderately depressed patients whom they compared with 13 normal control subjects. In a retrospective study, Kronfol

et al. (68) showed that depression was associated with a neutrophilia and a lymphocytopenia, analogous to those noted in Cushing's disease. They speculated that hypercortisolism could underlie the common immunologic abnormalities noted in these two disorders. Kronfol et al. (69) prospectively replicated these findings of neutrophilia and lymphocytopenia in a group of hypercortisolemic depressed patients whose cortisol levels were not suppressed following dexamethasone administration, but were unable to do so in depressed subjects who suppressed normally.

Studies of immunocompetence during depression have not yielded conclusive findings. Possible reasons for this lack of agreement may have to do with the experimental design of the studies and the immunologic assays themselves. Depression-related anorexia, weight loss, and malnutrition, as well as sleep deprivation resulting from illness-related insomnia, have been difficult to control for and make the data difficult to interpret (53-58). Likewise, these in vitro assays usually require freshly prepared suspensions of mononuclear cells, a factor which frequently means that patients and control subjects have their immunocompetence assessed at different times, depending on when they were recruited and their drug-free status. All of these variables, as well as disparity in severity of illness, make it difficult to compare one study with another.

It should be noted that the immunologic abnormalities seen in depression are very similar to those noted in bereaved and chronically stressed people. Hence,

theoretically, depressed individuals could also be vulnerable to the same kinds of illnesses—those which are avoided by intact cellular immunity (viral and fungal infections, malignant diseases, etc.) Surprisingly, however, in contrast to the number of retrospective epidemiologic studies of stressed and bereaved individuals, to our knowledge there have been few reports evaluating increased vulnerability to specific disease entities in subjects with depressive illness (70).

### The Role of Glucocorticoids in Immunomodulation

An association between hypercortisolism and diminished immunocompetence during stress, bereavement, and depression constitutes one of the few recurring themes in the clinical papers we have summarized. In this section we review the many immunity-modulating properties of glucocorticoids and attempt to evaluate the possibility that these hormones play a governing role in the immunologic deficits which have been reported in the psychiatric literature.

The importance of glucocorticoids in immunologic regulation was emphasized by Munck et al. (71), who concluded that the most important physiological effect of glucocorticoid secretion is to suppress the immune system. This counterregulatory effect of glucocorticoids on immune function, they argued, evolved because of the necessity for quickly terminating the robust inflammatory and/or immune response to injury that is expected during stressful "fight or flight" situations. Experimental support for this hypothesis derives from studies which show that adrenalectomized animals subjected to experimentally induced inflammation have a far higher mortality rate than control animals because of a prolonged, profound overactivity of their immunologic apparatus (unpublished observations of R. Flower et al.).

A comprehensive review of the immunosuppressive effects of glucocorticoids reveals that these effects are directed mainly at cell-mediated immunity (i.e., depression of T cell function). By an unknown mechanism, helper T cell function is preferentially affected, while suppressor T cell function remains intact (72– 74). This sparing of the effector cells, which act to limit the immunologic response, is compatible with the notion that glucocorticoids act to counterregulate the response to foreign antigens or injury (71). Glucocorticoids interfere with helper T cell function by several interrelated mechanisms. For instance, glucocorticoids inhibit the secretion of several lymphokines, including interleukin-1 (lymphocyte activating factor) (75), interleukin-2 (T cell growth factor) (76, 77), and  $\gamma$ interferon (macrophage activating factor) (71) (see figure 2). Through effects on lymphocyte activation, proliferation, and macrophage lytic activity, glucocorticoids interfere with components of the immunologic apparatus that subserve antiviral, antifungal, and tumoricidal activities.

Glucocorticoids also exert immunosuppressive effects through their impact on neutrophil function.

Glucocorticoids reduce migration of neutrophils to the site of injury or antigenic challenge, an effect that could contribute to the characteristic neutrophilia associated with glucocorticoid excess (78, 79). Glucocorticoids also cause monocytopenia (80, 81) and cosinopenia (82). Because monocytes are the circulatory precursors of tissue macrophages, such an effect could then impair antigen recognition by lymphocytes and macrophage-mediated phagocytosis.

Theoretically, the predominance of T over B cell abnormalities in stress, bereavement, and depression could be mediated by glucocorticoid excess. For instance, the abnormal lymphocyte repsonses to mitogens and allogeneic stimulation seen in stress and depression could involve a glucocorticoid-induced decrease in interleukin-2. Other abnormalities seen in stress and depression that are attributable to glucocorticoids include decreased natural killer cell activity, total lymphocytes, T cell lymphocytes, helper T cells, monocytes, and eosinophils and a neutrophilia. It should be noted, however, that it has not been definitively established that glucocorticoids mediate all of these abnormalities. For instance, in the important study of Keller et al. (83), stressed adrenalectomized animals, unlike stressed control animals, showed a persistent blunting of lymphocyte responses to T cell mitogens, although the stress-induced lymphocytopenia was resolved in the absence of glucocorticoid ex-

### The Role of the CNS in Immunomodulation

The preceding sections reviewing evidence for diminished immunocompetence during stress and depression suggest a role for the CNS in modulating the immunologic apparatus. A specific mechanism by which stress and depression influence the immune system seems to be neuroendocrine secretion mediated by the HPA axis. However, it should be emphasized that there are a variety of mechanisms by which the CNS could influence immune function, and any of these could theoretically contribute to the alterations in immune function noted in stress and depression. For instance, the recently demonstrated presence of neuroendocrine amine precursor uptake and decarboxylation (APUD) cells within various lymphoid organs suggests a further link between the neuroendocrine and immune systems (84). Moreover, hormones of the hypothalamic-pituitary-gonadal axis depress lymphocyte responses to antigen challenge by means of specific receptor-mediated mechanisms (85, 86). Conversely, growth hormone, insulin, and thyroxine enhance cellular immunity (87). β-Endorphin, which is co-secreted with ACTH from the anterior pituitary, has been shown to specifically enhance natural killer cell activity (88). This immunologic effect has been thought to be one of the principal roles of peripherally secreted β-endorphin.

Autonomic signals from the brain also influence immune function. Perivascular nerve plexuses are

known to surround lymphocytes in the spleen (89). In some instances, single noradrenergic fibers surround single lymphocytes in the spleen. Surgical denervation of the spleen and chemical sympathectomy lead to enhanced immunocompetence (90, 91). Moreover, catecholaminergic spillover during sympathetic activity may also affect immunocompetence. Norepinephrine and epinephrine are well-known immunity modulators (90, 91). A familiar example of the phenomenon is the dramatic effect of epinephrine in terminating acute anaphylactic reactions.

There are data to support the novel concept that immunocompetence can be influenced by the neuronal and/or neuroendocrine events which appear in association with learning. For instance, Ader and Cohen (92) applied a taste-aversion conditioning paradigm to animals, in which they paired an unconditioned stimulus (the immunosuppressant cyclophosphamide) with a drink distinctly flavored by saccharin, a substance with no known immunity-modulating properties (the conditioned stimulus). When the animals were given saccharin alone at a later time, they displayed a compromised, "immunosuppressed" response to a standard

antigenic challenge.

More recently, these investigators (93) examined the therapeutic impact of conditioned immunosuppression on the spontaneous development of systemic lupus erythematosus in New Zealand mice, hybrids that typically develop lethal renal complications of this illness by 12 months of age. By pairing cyclophosphamide (the unconditioned stimulus) with saccharin (the conditioned stimulus) and then later reexposing these mice to saccharin alone, Ader and Cohen were able to demonstrate that the conditioned stimulus had developed therapeutic immunosuppressant properties, as these mice lived longer and had a reduced morbidity. These data illustrate yet another potential means by which the central nervous system communicates with peripheral immunocytes to influence immune function.

The immunologic apparatus not only receives signals from the brain but transmits signals to the brain as well. For instance, such soluble products of the immune system as thymosins not only regulate immunity directly but, in addition, serve as "immunotransmitters" by modulating the HPA and gonadal axes (94). It is thought that this lymphoid/endocrine information provides the brain with data derived from contact between immunocytes and various antigens or tumors. In this regard, circulating lymphocytes can be seen as "sensory organs," converting information derived from contact with pathogens to useful endocrine signals for the brain (95). Such information could influence behavioral or physiological processes that adapt during infection or injury. Examples of the putative effects of the immunologic apparatus on brain function include evidence of decreased norepinephrine turnover (96) and increased firing of specific hypothalamic nuclei (97) during antigenic challenge. Concomitant with these changes is a decreased norepinephrine content in peripheral lymphoid organs during the immune response (90).

In addition to exerting effects on brain function through endocrine secretion, immunocytes may also exert humoral-mediated effects on peripheral endocrine function. For instance, lymphocytes have been shown to contain ACTH for direct stimulation of the adrenal cortex (98, 99). Indeed, this phenomenon suggests the possible existence of a lymphoid-adrenal axis to complement the HPA axis (100). This richness of diversity of communication between the immune system and both the CNS and the endocrine system is not surprising. A system as critical for survival as the immune system must be able to interact bidirectionally with both of these important integrative systems.

#### **FUTURE RESEARCH**

A challenge for psychiatry is to more fully characterize the effects of psychological states on specific components of immune function. A more difficult, but perhaps no less important, challenge for psychiatry is to characterize the mechanisms by which various components of the immune response influence brain, behavior, and mood. Such work will require the integration of the efforts of skilled clinicians, clinical researchers, and basic scientists. At present, there can be no firm conclusions about the clinical implications of data suggesting immunocompromise during stress, bereavement, and depression. In vitro immunologic studies have suggested that lymphocytes taken from stressed and/or depressed patients do not reproduce as well when challenged by an antigen. It should be noted, however, that there is little evidence of anergy on skin testing, which suggests that the cellular arm of the immune response remains largely intact.

Only retrospective studies have been conducted to assess depressed patients' vulnerability to disease. A prospectively designed study is needed, not only to assess quantitative and qualitative evidence of immunocompromise but also to comment on pathophysiology and clinical relevance. The complex interdependence and redundance of the different components of the immunologic apparatus, as well as the rate at which new basic immunologic information is being generated, provide a further challenge in this area. As lymphokines and other soluble mediators of the immune response take their place not only as important immunomodulators but as immunotransmitters, so must our understanding of their roles in psychological stress and psychiatric illness evolve. These "immunotransmitters" are likely to mediate the bidirectional exchange of information between the CNS and the immunologic apparatus, while possibly possessing mood-altering properties of their own. Future work in this area should enrich and further unify concepts about the interrelationships between the major mechanisms of integration available to complex living organisms.

#### REFERENCES

- 1. Metchnikoff E: Untersuchungen uber du intracellulare Verdaung bei werbellosen Tieren. Arb Zoologischen Inst Univ Wien 1883; 5:141-168
- 2. Ehrlich P: On immunity with special reference to cell life. Proc R Soc London (Biol) 1906; 66:424-430
- 3. Katz DH: The immune system: an overview, in Basic and Clinical Immunology, 6th ed. Edited by Stites DP, Stobo JD, Fudenberg HH, et al. Los Altos, Calif, Lange Medical Publications, 1987
- 4. Le Douarin NM, Jotereau FV: Tracing of cells of the avian thymus through embryonic life in interspecific chimeras. J Exp Med 1975; 142:17-40
- 5. Goldstein AL, Low TLK, Thurman GB, et al: Current status of thymosin and other hormones of the thymus gland. Recent Prog Horm Res 1981; 37:369-415
- 6. Gathings WE, Lawton AR, Cooper MD: Immunofluorescent studies of the development of pre-B cells, B lymphocytes and immunoglobulin isotype diversity in humans. Eur J Immunol 1977; 7:804-810
- 7. Glick B, Chang TS, Jaap RG: The bursa of Fabricius and antibody production. Poultry Science 1956; 35:224-225
- 8. Kehrl JH, Muraguchi A, Butler JL, et al: Human B cell activation, proliferation and differentiation. Immunol Rev 1984; 78:75-96
- 9. Burnet FM: A modification of Jerne's theory of antibody production using the concept of clonal selection. Aust J Sci 1957; 20:67-69
- 10. Rosen FS, Cooper MD, Wedgwood RJ: The primary immunodeficiencies, I. N Engl J Med 1984; 311:235-242
- 11. Bellanti JA, Artenstein MS: Mechanisms of immunity to virus infection. Pediatr Clin North Am 1964: 11:558-569
- 12. Spiegelberg HL: Biological activities of immunoglobulins of different classes and subclasses. Adv Immunol 1974; 19:259-
- 13. Porter RR, Reid KBM: The biochemistry of complement. Nature 1978; 275:699-704
- 14. Hanson LA, Ahlstedt S, Anderson B, et al: The biological properties of secretory IgA. J Reticuloendothelial Society 1980; 28 (suppl):1S-9S
- 15. Lichtenstein LM, Norman PS: Human allergic reactions. Am J Med 1969; 46:163-171
- 16. Cooper DA, Petts V, Luckhurst E, et al: T and B cell populations in blood and lymph node in lymphoproliferative disease. Br J Cancer 1975; 31:550-558
- 17. Bernard A, Boumsell L: The clusters of differentiation (CD) defined by the First International Workshop on Human Leukocyte Differentiation Antigens. Hum Immunol 1984; 11:1-
- 18. Gillus S: Interleukin-2: biology and biochemistry. J Clin Immunol 1983; 3:1-13
- 19. Fauci AS, Macher AM, Longo DL, et al: NIH conference: acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. Ann Intern Med 1984; 100:92-106
- 20. Govaerts A: Cellular antibodies in kidney homotransplantation. J Immunol 1960; 85:516-522
- 21. Wandlann TA, Balese RM, Broder S, et al: Disorders of suppressor immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. Ann Intern Med 1978; 88:226-238
- 22. Greenberg AM, Playfair JH: Spontaneously arising cytotoxicity to the P-815 mastocytoma in NZB mice. Clin Exp Immunol 1974; 16:99-110
- 23. Cerrottini JC, Brunner KT: Cell-mediated cytotoxicity, allograft rejection and tumor immunity. Adv Immunol 1974; 18:67-132
- 24. Simmons RL, So SKS: Clinical transplantation, in Basic and Clinical Immunology, 6th ed. Edited by Stites DP, Stobo JD, Fudenberg HH, et al. Los Altos, Calif, Lange Medical Publications, 1987
- 25. Herberman RB, Ortaldo JR: Natural killer cells: their role in

- defenses against disease. Science 1981; 214:24-30
- 26. Krim M: Towards tumor therapy with interferons (parts 1 and 2). Blood 1980; 55:711-721, 875-884
- 27. Babior BM: Oxygen dependent microbial killing by phagocytes. N Engl J Med 1978; 298:659-668
- 28. Rosen B: The origins, kinetics and fate of macrophage population. J Reticuloendothelial Society 1970; 8:139-161
- 29. Pierce CW: Macrophages: modulators of immunity. Am J Pathol 1980; 98:10-28
- 30. Oppenheim JJ, Stadler BM, Siranganian RP, et al: Lymphokines: their role in lymphocyte responses-properties of interleukin-1. Fed Proc 1982; 41:257-262
- 31. David JR, David RR: Cellular hypersensitivity and immunity: inhibition of macrophage migration and the lymphocyte mediators. Prog Allergy 1972; 16:300–449
  32. Schrieber RD, Pace JL, Russell SW, et al: Macrophage activat-
- ing factor produced by a T cell hybridoma: physiochemical and biosynthetic resemblance to gamma interferon. J Immunol 1983; 131:826-832
- 33. Sasazuki T, Nishimura Y, Muto M, et al: HLA-linked genes controlling immune response and disease susceptibility. Immunol Rev 1983; 70:51-75
- 34. Mittal KK: Human histocompatibility antigens. J Scientific and Industrial Research 1979; 38:37-46
- 35. Weitkamp LR, Stancer HC, Persad E, et al: Depressive disorders and HLA: a gene on chromosome 6 that can affect behavior. N Engl J Med 1981; 305:1301-1306
- 36. Kruger SD, Turner WJ, Kidd KK: The effects of requisite assumptions on linkage analyses of manic depressive illness
- with HLA. Biol Psychiatry 1982; 17:1081-1099
  37. Bartrop RW, Luckhurst E, Lazarus L, et al: Depressed lymphocyte function after bereavement. Lancet 1977; 1:834-836
- 38. Schleifer SJ, Keller SE, Camerino M, et al: Suppression of lymphocyte stimulation following bereavement. JAMA 1983; 250:374-377
- 39. Linn MW, Linn BS, Jensen J: Stressful events, dysphoric mood, and immune responsiveness. Psychol Rep 1984; 54:219-222
- 40. Kiecolt-Glaser JK, Ricker D, George J, et al: Urinary cortisol levels, cellular immunocompetence, and loneliness in psychiatric inpatients. Psychosom Med 1984; 46:15-23
- 41. Kiecolt-Glaser JK, Garner W, Speicher C, et al: Psychosocial modifiers of immunocompetence in medical students. Psychosom Med 1984; 46:7-14
- 42. Dorian BJ, Garfinkel PE, Brown G, et al: Aberrations in lymphocyte subpopulations and functions during psychological stress. Clin Exp Immunol 1980; 50:132-138
- 43. Locke SE, Kraus L, Leserman J, et al: Life change stress, psychiatric symptoms, and natural killer cell activity. Psychosom Med 1984; 46:441-453
- 44. Linn BS, Jensen J: Age and immune response to a surgical stress. Arch Surg 1983; 118:405-409
- 45. Schleifer SJ, Keller SE, Siris SG, et al: Depression and immu-
- nity. Arch Gen Psychiatry 1985; 42:129–133
  46. Meyer RJ, Haggerty R: Streptococcal infections in families: factors altering individual susceptibility. Pediatrics 1962; 29: 539-549
- 47. Kasl SV, Evans AS, Niederman JC: Psychosocial risk factors in the development of infectious mononucleosis. Psychosom Med 1979; 41:445-466
- 48. Baker GHB, Brewerton DA: Rheumatoid arthritis: a psychiatric assessment. Br Med J 1981; 282:2014
- 49. Sklar LS, Anisman H: Stress and cancer. Psychol Bull 1981; 89:369-406
- 50. Clot J, Charmasson E, Brochier J: Age-dependent changes of human blood lymphocyte subpopulations. Clin Exp Immunol 1972; 32:346-351
- 51. Kishimoto S, Tomino S, Inomata K, et al: Age-related changes in the subsets and functions of human T lymphocytes. J Immunol 1978; 121:1773-1780
- 52. Palmblad J, Cantell K, Strander H, et al: Stressor exposure and immunologic response in man: interferon-producing capacity and phagocytosis. J Psychosom Res 1976; 20:193-199
- 53. Palmblad J, Petrini B, Wasserman J, et al: Lymphocyte and

- granulocyte reactions during sleep deprivation. Psychosom Med 1979; 41:273–278
- Eskola J, Rauskanen O, Soppi E, et al: Effect of sport stress on lymphocyte transformation and antibody formation. Clin Exp Immunol 1978; 32:339–345
- Bistrian BR, Blackburn GL, Schrimshaw NS, et al: Cellular immunity in semi-starved states in hospitalized adults. Am J Clin Nutr 1975; 28:1148–1155
- Chandra RK: Numerical and functional deficiency in T helper cells in protein energy malnutrition. Clin Exp Immunol 1983; 51:126–132
- 57. Beisel WR, Edelman R, Nauss K, et al: Single-nutrient effects on immunologic functions. JAMA 1981; 245:53-58
- Miller LG, Goldstein G, Murphy M, et al: Reversible alterations in immunoregulatory T cells in smoking. Chest 1982; 82:526-529
- Watson RR, Eskelson C, Hartman BR: Severe alcohol abuse and cellular immune functions. Ariz Med 1984; 41:665–668
- Lazzarin A, Mella L, Trombini M, et al: Immunologic status in heroin addicts: effects of methadone maintenance treatment. Drug Alcohol Depend 1984; 13:117–123
- Kronfol Z, Silva J, Greden J, et al: Impaired lymphocyte function in depressive illness. Life Sci 1983; 33:241–247
- Schleifer SJ, Keller SE, Meyerson AT, et al: Lymphocyte function in major depressive disorder. Arch Gen Psychiatry 1984; 41:484

  486
- Sengar DPS, Waters BGH, Dunne JV, et al: Lymphocyte subpopulations and mitogenic responses of lymphocytes in manic depressive disorders. Biol Psychiatry 1982; 17:1017– 1022
- 64. Calabrese JR, Skwerer RG, Barna B, et al: Depression, immunocompetence, and prostaglandins of the E series. Psychiatry Res 1986; 17:41-47
- Goodwin JS, Webb DR: Review: regulation of the immune response by prostaglandins. Clin Immunol Immunopathol 1980; 15:106–122
- 66. Hedge GA: Roles for prostaglandins in the regulation of anterior pituitary secretion. Life Sci 1977; 20:17-34
- Albrecht J, Helderman JH, Schlesser MA, et al: A controlled study of cellular immune function in affective disorders before and during somatic therapy. Psychiatry Res 1985; 15:185– 193
- Kronfol Z, Turner R, Nasrallah H, et al: Leukocyte regulation in depression and schizophrenia. Psychiatry Res 1984; 13:13–
- Kronfol Z, Nasrallah HA, Chapman S, et al: Depression, cortisol metabolism, and lymphocytopenia. J Affective Disord 1985; 9:169–173
- Shekelle RB, Raynor WJ, Ostfeld AM, et al: Psychological depression and 17-year risk of death from cancer. Psychosom Med 1981; 43:117–125
- 71. Munck A, Guyre PM, Holbrook NJ: Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984; 5:25–44
- 72. Dupont E, Schandene L, Devos R, et al: Depletion of lymphocytes with membrane markers of helper phenotype: a feature of acute and chronic drug-induced immunosuppression. Clin Exp Immunol 1983; 51:345–350
- Glasser L, Hicks MJ, Lindberg RE, et al: The effect of in vivo dexamethasone on lymphocyte subpopulations: differential response of EAhu rosette-forming cells. Clin Immunol Immunopathol 1981; 18:22–31
- Haynes BF, Fauci AS: The differential effect of in vivo hydrocortisone on the kinetics of subpopulations of human peripheral blood thymus-derived lymphocytes. J Clin Invest 1978; 61:703-707
- Snyder DS, Unanue ER: Corticosteroids inhibit murine macrophage Ia expression and interleukin 1 production. J Immunol 1982; 129:1803–1805
- 76. Gillis S, Crabtree GR, Smith KA: Glucocorticoid-induced inhibition of T cell growth factor production, I: the effect on

- mitogen-induced lymphocyte proliferation. J Immunol 1979; 123:1624–1631
- 77. Gillis S, Crabtree GR, Smith KA: Glucocorticoid-induced inhibition of T cell growth factor production, II: the effect on in vitro generation of cytolytic T cells. J Immunol 1979; 123: 1632–1638
- 78. Boggs DR, Athens JW, Cartwright GE, et al: The effect of adrenal glucocorticosteroids upon the cellular composition of inflammatory exudates. Am J Pathol 1964; 44:763–773
- inflammatory exudates. Am J Pathol 1964; 44:763–773
  79. Dale DC, Fauci AS, Wolff SM: Alternate-day prednisone: leukocyte kinetics and susceptibility to infections. N Engl J Med 1974; 291:1154–1158
- Fauci AS, Dale DC: The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. J Clin Invest 1974; 53: 240–246
- 81. Fauci AS, Dale DC: Alternate-day prednisone therapy and human lymphocyte subpopulations. J Clin Invest 1975; 55: 22–32
- 82. Andersen V: Autoradiographic studies of eosinophil kinetics: effects of cortisol. Cell Tissue Kinet 1969; 2:139
- Keller SE, Weiss JM, Schleifer SJ, et al: Stress-induced suppression of immunity in adrenalectomized rats. Science 1983; 221: 1301–1304
- 84. Angeletti RH, Hickey WF: A neuroendocrine marker in tissues of the immune system. Science 1985; 230:89–90
- 85. Grossman CJ: Regulation of the immune system by sex steroids. Endocr Rev 1984; 5:435-455
- 86. Grossman CJ: Interactions between the gonadal steroids and the immune system. Science 1985; 227:257-261
- 87. Besedovsky HO, del Rey AE, Sorkin E: Neuroendocrine immunoregulation, in Immunoregulation. Edited by Fabris W, Garaci E, Hadden J, et al. London, Plenum, 1983
- 88. Mathews PM, Forelich CJ, Sibbitt WL, et al: Enhancement of natural cytotoxicity by beta endorphin. J Immunol 1983; 130: 1658-1662
- Reilly D, McCuskey A, Miller L, et al: Innervation of the periarteriolar lymphatic sheath of the spleen. Tissue Cell 1979; 11:121-126
- Besedovsky HO, del Rey AE, Sorkin E, et al.: Immunoregulation mediated by the sympathetic nervous system. Cell Immunol 1979; 48:346–355
- nol 1979; 48:346-355
  91. Felten DL, Felten SY, Carlson SL, et al: Noradrenergic and peptidergic innervation of lymphoid tissue. J Immunol 1985; 135:755-765
- 92. Ader R, Cohen V: Behaviorally conditioned immunosuppression. Psychosom Med 1975; 37:333–340
- Ader R, Cohen V: Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science 1982; 215:1534–1536
- 94. Hall NR, McGillis JP, Spangelo BL, et al: Evidence that thymosin and other biological response modifiers can function as neuroactive immunotransmitters. J Immunol 1985; 135: 806-811
- 95. Blalock JE: The immune system as a sensory organ. J Immunol 1984; 132:1067–1070
- Besedovsky HO, del Rey AE, Sorkin E, et al: The immune response evokes changes in brain noradrenergic neurons. Science 1983; 221:564–566
- 97. Besedovsky HO, Sorkin E, Felix D, et al: Hypothalamic changes during the immune response. Eur J Immunol 1977; 7: 323-325
- Smith EM, Blalock JE: Human lymphocyte production of corticotropin and endorphin-like substances: association with leukocyte interferon. Proc Natl Acad Sci USA 1981; 78:7530– 7534
- Blalock JE, Smith EM: Human leukocyte interferon: structural and biological relatedness to adrenocorticotropic hormone and endorphins. Proc Natl Acad Sci USA 1980; 77:5972– 5974
- Smith EM, Meyer WJ, Blalock JE: Virus-induced corticosterone in hypophysectomized mice: a possible lymphoid adrenal axis. Science 1982; 218:1311–1312

# Current Status and Future Directions of Research on the American Indian Child

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American Indians are the most severely disadvantaged of any population within the United States. By adolescence, Indian children show higher rates of suicide, alcoholism, drug abuse, delinquency, and out-of-home placement. School achievement is severely compromised, and many youths drop out before graduation from high school. The Indian child understands the environment through intuitive, visual, and pictorial means, but success in the Anglo school is largely dependent on auditory processing, abstract conceptualization, and language skills. This difference compounds existing problems of poverty, dislocation, alienation, depression and intergenerational conflict and can partially account for the higher rate of emotional and behavioral problems among Indian adolescents.

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On the whole, American Indian tribes are remarkable in that they have withstood attempts at extermination, removal from their traditional lands, extreme poverty, deployment of their youth to boarding schools, relocation policies, and, last but not least, the white man's poison—alcohol. In spite of this, the tribes remain ethnically distinct in cognitive style, language forms, art, and culture. Although there are many similarities among tribes and, in this article, Indians will frequently be referred to as a homogeneous people, the tribes are actually quite heterogeneous.

For centuries, American Indians have existed as hunters and gatherers, living off the none-too-fertile land. They became uniquely adapted to that style, developing skills which enabled them to survive. Now, American Indians are expected to "acculturate," which may mean abandoning all that is sacred and unique in their traditional life style. This expectation entails considerable stress and the risk of identity diffusion. The plight of the partially acculturated Amer-

ican Indian is epitomized by the Iroquois saying, "One cannot long have one's feet placed in two canoes." This quotation, in itself, is a succinct graphic metaphor, creating in our minds a rich visual picture of a concept that would entail many words. The graphic metaphor is also the cognitive language of the American Indian.

In 1900 there were 220,000 Indians in the United States; today there are somewhere between 1 and 2 million Indians in approximately 400 recognized tribes, 180 of which have a land base such as a reservation. One-third of the Indian population live on reservations, one-third are urban, and one-third move back and forth between town and reservation (1). The median age of the Indian population is 17.3 years; in the United States as a whole the median age is 29.5 years (2). This discrepancy is primarily accounted for by the birth rate among Indians, which is twice as high as that of the country at large. The death rate in certain age groups is also extraordinarily high: among 5-24-year-old Indians the death rate is two to three times higher than it is in the United States as a whole (3), and the infant mortality is the highest of any ethnic group in the United States. Twenty percent of all deaths among American Indians occur in infants and young children (2).

The disability rate among American Indians is four to six times the national average. Diabetes and the complications of alcoholism are the sources of the greatest disability among adults, and hepatitis B infection and otitis media contribute to children's disabilities (2, 4). The average income of Indian families is \$2,000/year, far below the poverty level. On the reservation, the mean average income is only \$900/year, well below a bare level of subsistence. Of necessity, many Indians continue to supplement this meager allotment through hunting and gathering. The overall unemployment rate is 40%, but it is as high as 75%—90% on some reservations (1). Thus, the American Indian is the most severely disadvantaged population within the United States.

# MENTAL HEALTH PROBLEMS AMONG INDIAN CHILDREN

The overall rate of emotional disorders in childhood among American Indians is 20%-25% (2), compared

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with 5%-15% among children in the Anglo population. However, these figures must be held suspect because national statistical comparisons are usually based on small-scale tribal studies and rates of emotional disorder vary dramatically among tribes and among regions. However, there does seem to be a fascinating pattern of variance—among Indian children 5–9 years old, the rate of emotional disturbance is approximately the same as it is in the majority culture; problems consist of both learning and behavioral difficulties (5). Between ages 10 and 14 the emotional disorder rate in Indian children begins to escalate and includes delinquency and drug use as well as learning and behavioral problems. Whereas only 9% of youths in the majority culture have abused inhalants, 22% of Indian youths have abused them (6). By far the greatest number of emotional problems occur between ages 15 and 19: problems of drug and alcohol abuse and delinquency in males and unwanted pregnancy, alcohol abuse, and suicide attempts in females (5). Many authors (2, 7, 8) have described profound alienation and depression in Indian adolescents, although, once again, there is marked variation between tribes.

Alcohol abuse is an extensive and pervasive problem for the Indian. The overall rate of alcoholism is two to three times the national average (9, 10), although the rate varies widely among tribes. The rate of recent alcohol use is 50% among Indian adolescents and 20% in the majority culture (6). It is not uncommon to find children as young as 6 years old already drinking alcohol (11). Among adolescents, alcohol abuse is a normative pattern that facilitates interaction (5) and reduces psychological distress (8). To refuse a drink when it is offered is to insult the one who offers; the person who refuses is thought to be acting superior, like a white man (12). Solitary drinking is infrequent, but rapid drinking to become intoxicated is common. In some areas, being drunk becomes equivalent to being possessed by a spirit, which relieves the intoxicated person from responsibility for antisocial acts (13). Because of the cultural policy of noninterference, adults seldom intervene in the drinking behaviors of their children.

Associated with alcohol abuse is an inordinate number of accidents: 75% of accidents are alcohol related, 80% of suicides are alcohol related, and 90% of homicides are alcohol related (14). In addition, alcohol-abusing adolescents often become alcoholic parents who tend to neglect their children and become involved in domestic violence (11). They are also three to four times as likely as members of the majority culture to succumb to cirrhosis of the liver and other complications of alcohol abuse (14). The suicide rate among Indians peaks in the adolescent and young adult years (15, 16) and is the second major cause of death in adolescence. There is substantial variation among tribes (15, 17); rates are higher in dislocated tribes where members are unable to practice the traditional life style. The suicide rate has remained low on a few reservations where traditional practices are

maintained and where adolescents can attend school and work within the tribal community (18).

During adolescence, 12 of every 100 Indian youths and 2.5 of every 100 adolescents in the majority culture appear in court. The Indian youths are more likely to appear because of misdemeanors or petty offenses that are alcohol related (19). When the court appearances are controlled for alcohol intoxication, the rates are approximately the same in both cultures (9).

In spite of a common assumption to the contrary, very few Indian children are abused: 6.5/1,000 Indian boys and 2.7/1,000 Indian girls suffer maltreatment, compared with 13/1,000 black children and 15/1,000 white children (20, 21). Physical punishment is frowned upon in most Indian communities, and children are protected through informal placement within the extended family, a major resource for Indian youngsters. Most maltreated Indian children are neglected rather than physically abused (20), which is not surprising given the level of poverty on Indian reservations. In addition, Indian parents may be interpreted as neglectful by Anglo agency workers because of cultural differences (22). In some instances, the maltreatment is directly related to the alcohol abuse of one or both parents.

In spite of the lower rate of child maltreatment, five to 20 times as many Indian children as children in the culture as a whole are in out-of-home placements (23, 24). In 1976, almost 50,000 Indian children resided in boarding schools, foster homes, and adoptive homes (25). As many as 85% of these placements were in non-Indian residences (23), thus occasioning a profound rupture of cultural ties (26). "Poverty" was the most frequent rationale for out-of-home placement (27). Placement in boarding schools has been related to the unavailability of day schools in isolated areas of reservations, especially among the Navajo, 10,000 of whose elementary schoolchildren are now boarded (4). Other students are at boarding school because of the lack of adoptive or foster home placements for older, often psychiatrically disturbed, youths. The rate of psychiatric disorders is higher among children placed outside their homes (28; unpublished 1978 paper by M.D. Topper), but this may be either a cause or an effect of the placement. To date there has been no controlled outcome study of out-of-tribe versus intribe placement and how this variable might influence the quality of attachment and incidence of emotional disorder.

Many Indian children who live in isolated villages are never registered in public school but are taught by using whatever resources are available. A number of other children are enrolled in school but do not attend due to lack of transportation or insufficient motivation. It is likely that children who do attend school will drop out before finishing the program. The dropout rate in boarding school is 60% (29), in high school it is almost 50%, and in college it is 70% (30). There have been fewer Indian youths enrolled in government-

funded boarding schools in the past decade, and there has been an effort to improve the quality of life of the Indian child who boards (31). However, as many as 75% of the boarders are said to suffer from emotional problems, alienation, and feelings of defeat and helplessness (32), perhaps related to the austere environment and to the children's attempts to match traditional values with those expected within the boarding school. When this is not possible, the result is a pattern of superficial responsiveness (33, 34). School dropouts often return to the reservation. These individuals may be reintegrated and lead productive lives, or they may continue to "drop out" on the reservation because of alcoholism, depression, and vocational failure.

To grow up as an Indian child is to grow up as a member of an extraordinarily disadvantaged minority. The pervasive emotional, physical, and social disabilities create a legacy of hopelessness and helplessness from which Indian youths must struggle to emerge. These disabilities stand as the penultimate predictors of a problematic future.

### **ACCULTURATION STRESS**

Acculturation is a critical process that involves multiple variables at the cultural, ethnic, interpersonal, and intrapersonal levels. Adaptive acculturation can be achieved by two means: by assimilation into the dominant culture, which means that one's original cultural identity is relinquished, or by integration, which means that the original cultural identity is retained. Assimilation and integration are considered adaptive approaches. The most maladaptive approach is the rejection of either the original or the dominant culture. Some individuals and groups become marginal, existing apart from either society. Although stress is not an inevitable concomitant of acculturation, it is accentuated when the cultural distance between the two groups is great and the insistence on change is strong (35). Greater stress is found in groups who resemble the majority culture the least, who do not have a great deal of contact with the majority culture, and who have been uprooted so that their traditional and social supports are disrupted. By these measures, Indians suffer considerable stress if they remain on the reservation with little cultural interchange and if they migrate to cities or are relocated away from their traditional lands.

Stress experienced by the family affects the children. Boggs (36), in a study of the Ojibwa, found that the children of "somewhat acculturated" families were more passive and less responsive than children of either traditional or acculturated families. The parents of somewhat acculturated children interacted less in the home and appeared less involved with the children. This may be an early symptom of an important component of acculturative stress: intergenerational conflict. Young people acculturate more rapidly as

they attend school and have greater contact with the majority culture. Because of their age, young people may be more open to change than are their parents. Parents feel abandoned and devalued in response to their children's greater acculturation. Studies of acculturating Hispanic families (37) demonstrated that the families with the greatest intergenerational conflict evidenced the most serious symptomatic behavior.

#### TRADITIONAL VALUES

If Indians, in the process of acculturation, espouse Anglo ways, they find themselves in conflict with the tribe. If they remain traditional, they may find themselves in conflict with the dominant culture, especially in the areas of sharing, allegiance, respect for elders, noninterference, orientation to present time, and harmony with nature.

# Sharing

Indian children are taught to share; competitive striving is inhibited and generosity is encouraged (38). Children are unwilling to compete because they do not wish to shame the person who loses. Children playing baseball on the Papago reservation hit the ball as many times as necessary. The score is not kept and team members are not selected on the basis of skill. Because of their reluctance to compete, Indian children in Anglo schools are often labeled as unmotivated or alienated. The reluctance to compete is situation specific; Indian children can be as fiercely competitive as anyone else when circumstances are conducive.

# Allegiance

Allegiance is to the family and the community rather than to the self. The youth who excels in terms of personal achievement may be ridiculed and rejected within the tribe. The following example was provided by G. Krutz.

Case 1. At 17 years of age, Charlie was about to graduate from high school. He was an excellent boxer and had become the state boxing champion. During a school assembly, the principal gave Charlie a special award accompanied by a long, impassioned congratulatory address. On the way out of the auditorium, a group of other Indian boys jumped on Charlie and pummeled him soundly. Charlie dropped out of school even though there was but 1 month to graduation.

# Respect for Elders

Children are taught not to question or to look directly at adults because this would be disrespectful. As this principle also applies to teachers within the school system, Indian children have been described as withdrawn, shy, or uninterested because they avoid eye contact and do not speak up (39).

# Noninterference

Indian children are not perceived as the property of their parents but as autonomous, equal individuals (40) who progress in life at their own inimitable pace and who are responsible for their own choices. Thus, toddlers choose when to eat or to sleep and gradeschool children may choose not to attend school. Older children may travel to the medical clinic by themselves (26) and may decide whether to have elective surgery (41). Since there is no "right" way to raise children, parents do not interfere with the expectable course of development (42, 43). Training in developmental tasks is encouraged and rewarded but not consciously taught or forced (unpublished 1967 report by J. Ablon et al.). Thus, many Indian parents have been described as neglectful or uninvolved when, in fact, they are concerned with their children's wellbeing (22).

## Orientation to Present Time

Indian children may not arrive at school on time, and Indian youth may not complete assignments or report for work as scheduled. These children, especially the girls, tend to live in and to value present time; deadlines are markers of future time (33; unpublished 1967 report by J. Ablon et al.). The following case vignette was supplied by G. Krutz.

Case 2. An Indian Health Service official received authorization for a mental health services contract, to be offered to the Papago Tribal Council. He presented the document to a Tribal Council member who was also an old friend. After perusing the document, the Indian representative indicated that he would "see about it." Six months passed. Because there was a deadline on the contract the Health Service official received many memos, but he refused to pressure or even to recontact his friend. In the meantime, the Tribal Council member was sitting with various families to discuss the pros and cons of mental health services in general. Finally, several months after the original deadline, he presented the signed contract to the Indian Health Service official.

Because of this disregard for deadlines, Indians have often been thought to be lazy or irresponsible. However, an Indian's disregard for deadlines is also context dependent, and the context often does not favor the Indian.

# Harmony With Nature

To the Indian, life should be an unhurried, natural progression (unpublished 1967 report by J. Ablon et al.). White men are viewed as tampering with and distorting nature. Disease, death, and disability are accepted as milestones in the course of life's progress.

Case 3. A new, rather officious medical social worker on an Indian reservation attempted to convince the women that their children should receive polio vaccine. In spite of her well-prepared presentation, which included statements like "You don't want them to get polio, do you?" the women did not bring their children to the clinic. They listened politely and sometimes giggled among themselves. Two years later, the social worker learned through another professional that the women had named her "Woman Who Can't Stop Talking."

Because of Indians' apparent disregard for the principles of the majority culture, they can be perceived as disconnected or as uncaring and irresponsible.

#### THE VISUAL MODE

An important and hitherto poorly understood source of acculturation stress is the differing cognitive style of American Indians. For centuries, the Indian peoples depended on the visual pathway. They followed animals by sign and track and memorized facets of the territory. Blending with the landscape, they moved silently through the forest to avoid their enemies. The women were able to single out edible plants from a mass of vegetation. Indians predicted changes in the weather and the migration of animals by studying the sky and the earth. The principle of observation was central in the culture.

The virtue of silence has been taught to Indian children from earliest infancy. Among the Plains Indians, when a newborn baby cried the parent would place a hand over the infant's nose so that the mouth would be needed for breathing (44). Chinese and Navajo infants will accept a cloth over the nose without protest, whereas Anglo and black infants will fight the cloth; they struggle and turn away. Certain Indian tribes use cradle boards, which inhibit the infant's movement toward objects (44) and may enhance the practice of looking at objects rather than grasping them. In some tribes, such as the Papago and the Yaqui, there is little conversation in the home. When children begin to speak, baby talk is discouraged and the child is expected to enunciate properly (40). Naughty children are shamed or ignored rather than talked to or yelled at as they would be in Anglo homes. Siblings and peers often teach younger children by nonverbal encouragement and example (unpublished 1978 paper by M.D. Topper). Societal norms may be presented through fables that are memorized and handed down from generation to generation. When a fable is related, children are encouraged to listen, to be sensitive to what others think, and to obey rather than to ask questions (45). Traditional ceremonies are passed down the generations through participation and example (unpublished 1978 paper by M.D. Topper). Learning is by trial and error. An Anglocized adolescent's questioning an elder becomes a source of frustration and bewilderment, and the youth may be sharply criticized.

The construction of the Indian language is unlike

that of the English language. Indian children's facility in English is among the poorest of any group in the United States; this is so even when they are reared in homes where English is spoken (40). The emphasis on observation and form is reflected in the language. For instance, in the Navajo native tongue the verb form may depend on the shape of the object of reference (46). Languages that stress form do not lend themselves readily to verbal abstractions, but they do augment the development of strategies involving the visual (graphic) metaphor, which can be viewed as a visual abstraction. Thus, it is extraordinarily difficult to translate abstractions between the Navajo and the English languages. Indian children may excel at the visual mode. For instance, Navajo children begin to sort by form rather than by color at an early age, attaining these norms in advance of other children. The most pronounced tendency to sort by form is found among the children who speak only Navajo (47).

There is evidence that the basic cognitive development of Indian children approximates that of the children of the majority culture; Piagetian tasks are attained at the expectable ages (48). Paiute children under age 2 meet expectable norms on the Gesell Developmental Profile, but their performance begins to decline as the verbal content of the scales becomes more prominent with increasing age (49). Choctaw Indian infants perform well above average on the Bayley Scale of Infant Development, a nonverbal measure, but fall below the average when they are tested later on by the McCarthy Index, a verbal measure (unpublished 1975 report by P. Quigley).

Indian children produce consistently low scores on the verbal scales of intelligence tests, but their scores on the performance scales approximate the norms of the majority culture. Boys tend to score approximately 5 points lower on the verbal scales. Children enrolled in certain Head Start programs have demonstrated marked gains (unpublished 1966 paper by H.L. Saslow), but these are not maintained when they enter the regular school system (50, 51). However, in regular schools, Indian children most often are taught by teachers who cannot speak their native tongue and who, in a subtle fashion, may be prejudiced against them.

That Indian children score within the average range on performance scales suggests that the Indian child's intelligence is intact but that our assessment instruments are biased toward verbal rather than performance skills. The tests are not culture free but depend on the language skills, competitive stance, and motivation of the children who are tested. However, in the dominant culture of the United States, academic and vocational success is largely dependent on language skills. Not only do Indian children not acquire language skills easily, but they become enmeshed in a cycle of depression, discouragement, and alienation that further impairs their test-taking ability. On the other hand, it has been shown that the performance of Indian children on

some subtests of the Wechsler test can be enhanced when the examiner communicates warmth nonverbally (52).

On entering school, Indian children experience problems with language, auditory association and memory, grammatic closure and auditory processing, reading, and verbal discrimination (53-55). Not only have a great many of the children not been exposed to English before entering school (56), but they may be totally unprepared to acquire English because of the different structure of the two languages. Problems in acquiring English are augmented by the fact that the Indian child has been trained to respect adults by not asking questions and by not looking directly at them. Thus, Indian children remain largely dependent on nonverbal clues to understand their environment, and they may appear passive and uninvolved in the learning process. The impairment in acquisition of language, auditory processing, and conceptualization has profound and persistent consequences, including the recently demonstrated strong association between language disorders and psychiatric problems (57).

In spite of difficulties with the auditory pathway and language, Indian children demonstrate an unusual ability to memorize visual patterns, visualize spatial concepts, and produce descriptions that are rich in visual detail and the use of graphic metaphors (58). Unfortunately, these skills count for little in the Anglo school system if the child is unable to remember or process verbal content. Indian children are hard put to recall content that is presented verbally and not portrayed visually (59). These deficits seem fundamental to what has been called the "crossover phenomenon" by which Indian children appear to do well in school until the third grade only to begin a progressive downhill course (9, 34). The higher the grade level that Indian children achieve, the greater is their lag in performance (30).

Indian children's representational function seems to be mediated visually rather than linguistically (59), and Indian children do not spontaneously analyze their experience in verbal terms (60) but, rather, absorb the experience as a whole, using intuitive, "right brain" mechanisms (61). They do not formulate or use logical constructs as their Anglo age-mates do but, on the other hand, are more aware of their environment (40, 62). The cards seem to be stacked against Indian children from the time they enter school, and their achievement deficits become increasingly apparent as they move through the school system. Achievement and emotional problems are interrelated—it is the children with low achievement scores who exhibit anomie and low self-esteem (34), and preschoolers with signs of emotional disturbance are more likely to see themselves as poor learners (63). The dissonance in cognitive style between the Indian child and the Anglo school must be a precipitating factor in the emergence of emotional problems, depression, hopelessness, alienation, and behavioral difficulties found among older Indian children and adolescents.

# INFECTIOUS AND NUTRITIONAL PROBLEMS

According to earlier estimates (64), 75% of all the Indian children were said to fall in the retarded range. Currently, 33% of Indian children are thought to have learning disabilities and 19% fall into the mentally retarded range (65), although even this figure is thought to be substantially influenced by cultural deprivation and test bias. The rate of learning problems and retardation is related to the fact that otitis media and nutritional problems are endemic on many reservations. A direct and significant relationship exists between the number of episodes of otitis media and the degree of hearing deficit and lower verbal scale scores on the WISC (66, 67). Most Indians living on a reservation are dependent on government surplus foods, which are high in carbohydrates and fats and low in protein and certain essential vitamins. Fruits, meats, and vegetables may be in short supply, too expensive, or unattractive to the Indian; this contributes to the incidence of malnutrition. Studies relating nutritional status with IQ and school performance certainly are in order.

#### **FUTURE RESEARCH DIRECTIONS**

Certain ethical considerations must be resolved before one considers directions for research. Historically, we have expected American Indian children to renounce the traditional way in order to acclimate to the majority culture. Children as young as 6 years old have been removed from their families and placed in government boarding schools so they might learn the "right" way; other children have been adopted by Mormon families interested in saving the "poor Indian" (unpublished 1978 paper by M.D. Topper). Should we continue our pressure cooker methods to coerce Indians to acculturate or should we promote the freedom of movement between cultures that would foster mutual enrichment? Clearly needed is a social policy that enhances constructive interchange, provides social supports, and militates against dislocation. Fortunately, individuals from among traditional and acculturated groups of Indians have emerged to become social and political activists. Organizations such as the Association on American Indian Affairs are lobbying to facilitate change, to increase funding, and to bring the control of social and political affairs back within the tribal community.

The complexity of the needs of various Indian groups indicates that we must place our feet squarely in three canoes: prevention, prediction, and intervention.

#### Prevention

Mental retardation and learning disability can be prevented to some extent. Otitis media and inadequate nutrition are likely culprits that need to be better defined and remedied. The Indian child's problem in acquiring language skills may stem from adaptive, genetic, or early environmental factors. Early environmental bases such as diminished use of language in the home may be ameliorated through early stimulation programs in which parents are encouraged to use language in interacting and playing with preschool children. It goes without saying that such programs will fail without substantial parent education and involvement as well as tribal endorsement. This cannot be achieved solely through the provision of government funding but needs to be implemented by Indian developmental specialists committed to the growth and well-being of the Indian people (68, 69). Indians themselves must determine their own priorities with respect to life style, occupational and social roles, the educational process, and the kinds of personal and social problems to be addressed by mental health professionals. No one other than the Indian people should determine how the individual, the tribe, and the nation should integrate with the majority culture and, at the same time, resist engulfment.

#### Prediction

If predictors of later social, emotional, and behavioral problems can be established for Indian children, appropriate interventions are more likely to evolve. Areas of investigation must include adaptive, genetic, and early environmental factors. This would necessitate a longitudinal study to compare the development of children reared on the reservation in the natural home with children adopted early in life and reared off the reservation in non-Indian families. Such a study would need to control for family disruption, number of child placements, socioeconomic status, adequacy of schooling, etc.

#### Intervention

Programs need to be developed to provide specialized aids to enhance the acquisition of language through developing diverse instructional approaches that combine visual, observational, and exploratory methods (59). These programs would also build an active, problem-solving approach to the acquisition of English (70) during early preschool and grade-school years. Teachers from the Indian culture or teachers knowledgeable about the Indian culture would be needed to offer interpersonal support, identification, and inspiration.

Programs to maximize the inherent potential of the Indian child should emphasize strengths rather than weaknesses, building on the exceptional abilities of the Indian child by individualized programs to develop fine motor, classification, visual-spatial, and visual-memory skills. Occupational training and fifth-pathway programs that begin in grade school might prepare Indian children for eventual success in such areas as forestry, art and design, interior decoration, crafts,

curatorship, ethnology, agriculture, and transportation.

#### **CONCLUSIONS**

A visually based cognitive style is an additional liability for the Indian child in the Anglo system. This problem, coupled with extreme physical, economic, and acculturation stressors, must contribute to the immense emotional and behavioral difficulties found among Indian children and adolescents.

#### REFERENCES

- American Indians, Subject Report, 1970 Census of the Population: PC(2)-IF. Washington, DC, US Department of Commerce, Census Bureau, 1973
- Wallace HM: The health of American Indian children. Health Serv Rep 1972; 87:867–876
- Kemberling SR: The Indian Health Service: commentary on a commentary. Pediatrics 1973; 51:6-9
- Association on American Indian Affairs: Program of Activities. New York, AAIA, 1986
- Beiser M, Attneave CL: Mental disorders among Native American children: rates and risk periods for entering treatment. Am J Psychiatry 1982; 139:193-198
- Goldstein GS, Oetting ER, Edwards R, et al: Drug use among Native American young adults. Int J Addict 1974; 14:855–860
- 7. Bryde JF: Indian Students and Guidance. Boston, Houghton Mifflin, 1971
- Holmgren C, Fitzgerald BJ, Carman RS: Alienation and alcohol use by American Indian and Caucasian high school students. J Soc Psychol 1983; 120:139–140
- Jensen GF, Strauss JH, Harris VH: Crime, delinquency and the American Indian. Human Organization 1977; 36:252–257
- Cockerham WC: Drinking attitudes and practices among Wind River Reservation Indian youth. J Stud Alcohol 1975; 36:321– 326
- 11. Kahn MW: Cultural clash and psychopathology in three aboriginal cultures. Academic Psychol Bull 1982; 4:553-561
- 12. Westermeyer J, Neider J: Cultural affiliation among American Indian alcoholics: correlations and change over a ten year period. J Operational Psychiatry 1985; 16:17–23
- Levy JE, Kunitz SJ: Indian Drinking: Navajo Practices and Anglo-American Theories. New York, John Wiley & Sons, 1974
- Cohen S: Alcohol and the Indian. Drug Abuse & Alcoholism Newsletter, May 1982
- McIntosh JL, Santos JF: Suicide among Native Americans: a compilation of findings. Omega 1981; 11:303–316
- May PA, Dizmang LH: Suicide in the American Indian. Psychiatr Annals 1974; 4:22–27
- 17. Dizmang LH, Watson J, May PA, et al: Adolescent suicide at an Indian reservation. Am J Orthopsychiatry 1974; 44:43–49
- Berlin IN: Suicide among American Indian adolescents, in Linkages for Indian Child Welfare Programs. Washington, DC, National American Indian Court Judges Association, 1984
- Forslund MA, Meyers RE: Delinquency among Wind River Indian Reservation youth. Criminology 1974; 12:97–106
- Nagi SZ: Child Maltreatment in the United States. New York, Columbia University Press, 1977
- 21. Oakland L, Kane RL: The working mother and child neglect on the Navajo Reservation. Pediatrics 1973; 51:849–853
- the Navajo Reservation. Pediatrics 1973; 51:849–853 22. Ishiasaka H: American Indians in foster care: cultural factors
- and separation. Child Welfare 1978; 57:299-308
  23. Mindell CE, Gurwitt A: The Placement of American Indian Children—the Need for Change. Washington, DC, American Academy of Child Psychiatry, 1977
- 24. Byler W: The destruction of American Indian families, in The

- Destruction of the American Indian Family. Edited by Unger S. New York, Association on American Indian Affairs, 1977
- Association on American Indian Affairs: Indian Child Welfare Statistical Report Submitted to the American Indian Policy Review Commission; US Congress, New York, AAIA, 1976
- Green HJ: Risks and attitudes associated with extra-cultural placement of American Indian children: a critical review. J Am Acad Child Psychiatry 1983; 22:63–67
- Westermeyer J: Cross-racial foster home placement among native American psychiatric patients. J Natl Med Assoc 1977; 69:231–236
- 28. Simon NM, Senturia AG: Adoption and psychiatric illness. Am J Psychiatry 1966; 122:858–868
- Beiser M: Étiology of mental disorders: socio-cultural aspects, in Manual of Child Psychopathology. Edited by Wolman B. New York, McGraw-Hill, 1972
- Zintz MV: The Indian Research Study, Final Report. Albuquerque, University of New Mexico College of Education, 1960
- 31. Goldstein GS: The model dormitory. Psychiatr Annals 1974; 4: 85-92
- Kleinfeld J, Bloom J: Boarding schools: effects on the mental health of Eskimo adolescents. Am J Psychiatry 1977; 134:411– 417
- 33. Krush TP, Bjork JW, Sindell PS, et al: Some thoughts on the formation of personality disorder: study of an Indian boarding school population. Am J Psychiatry 1966; 122:868–876
- 34. Saslow HL, Harrover MJ: Research on psychosocial adjustment of Indian youth. Am J Psychiatry 1968; 125:224–231
- Berry JW: Acculturation as varieties of adaptation, in Acculturation: Theory, Models and Some New Findings. Edited by Padilla AM. Boulder, Colo, Westview Press, 1979
- Boggs ST: An interactional study of Ojibwa socialization. Am Sociol Rev 1965; 21:191–198
- 37. Szapocznik J, Truss C: Intergenerational sources of role conflict in Cuban mothers, in Hispanic Families: Critical Issues for Policy and Programs in Human Service. Edited by Montiel M. Washington, DC, National Coalition of Hispanic Mental Health and Human Services Organizations, 1978
- Erikson EH: Childhood and Society, 2nd ed. New York, WW Norton, 1963
- 39. Philips SU: Participating structures and communicative competence: Warm Springs children in community and classroom, in Functions of Language in the Classroom. Edited by Cazden CB, John VP, Hymes D. New York, Teachers College Press, 1972
- Blanchard EL: The growth and development of American Indian and Alaskan Native children, in The Psychosocial Development of Minority Group Children. Edited by Powell GJ. New York, Brunner/Mazel, 1983
- 41. Clevenger J: Cultural aspects of mental health care for American Indians, in Cross-Cultural Psychiatry. Edited by Gaw A. Littleton, Mass, John Wright-PSG, 1981
- 42. Hallowell A: Culture and Experience. Philadelphia, University of Pennsylvania Press, 1955
- 43. Wax R, Thomas R: American Indians and white people, in Native Americans Today: Sociological Perspectives. Edited by Bahr H, Chadwick B, Day R. New York, Harper & Row, 1972
- 44. Neithhammer C: Daughters of the Earth: The Lives and Legends of American Indian Women. New York, Macmillan, 1977
- 45. Garcia V: An Examination of Early Childhood Education of the American Indian: A Relationship of Culture and Cognition. Albuquerque, University of New Mexico, 1974
- 46. Carroll JB, Casa Grande JB: The function of language classifications in behavior, in Readings in Social Psychology, 3rd ed. Edited by Maccoby EE, Hartley EO. New York, Holt, Reinhart and Winston, 1958
- 47. Spellman CM: The Shift From Color to Form Preference in Young Children of Different Ethnic Backgrounds. Austin, University of Texas Child Development Evaluation and Research Center, 1968
- 48. Silk S, Voyet G: Cross Cultural Study of Cognitive Development on the Pine Ridge Indian Reservation: Pine Ridge Research Bulletin Number 11, DHEW Publication HSM 80-69-430. Washington, DC, Indian Health Service, 1970

- Cazden CB, John VP: Learning in American Indian children, in Anthropological Perspective on Education. Edited by Wax NL, Diamond S, Gearing FO. New York, Basic Books, 1971
- Wolff M, Stein A: Six Months Later: A Comparison of Children Who Had Head Start, Summer, 1965, With Their Classmates in Kindergarten. New York, Yeshiva University Ferkauf Graduate School, 1966
- Homme LE: A System for Teaching English Literacy to Preschool Indian Children. Pittsburgh, Westinghouse Research Laboratories, Oct 11, 1965
- 52. Kleinfeld J: Effects of nonverbally communicated personal warmth on the intelligence test performance of Indian and Eskimo adolescents. J Soc Psychol 1973; 91:149–150
- Lombardi T: Psycholinguistic abilities of Papago Indian school children. Except Child 1970; 36:485–493
- 54. Trimble JE, Goddard A, Dinges NG: Review of the Literature on Educational Needs and Problems of American Indians, 1971 to 1976: DHEW Contract 300-76-0436. Seattle, Battelle Memorial Institute, Social Change Study Center, 1977
- McShane D: A review of scores of American Indian children on the Wechsler Intelligence Scales. White Cloud J 1980; 1:3–10
- Gold MJ: In Praise of Diversity: A Resource Book for Multicultural Education. Washington, DC, Association of Teacher Education, 1977
- 57. Beitchman JH, Nair R, Clegg M, et al: Prevalence of psychiatric disorders in children with speech and language disorders. J Am Acad Child Psychiatry 1986; 25:528-535
- Kleinfeld JS: Characteristics of Alaskan Native students, in Alaskan Native Needs Assessment in Education: Project ANNA. Juneau, Juneau Area Office, Bureau of Indian Affairs, 1974
- 59. John-Steiner V, Osterreich H: Learning Styles Among Pueblo

- Children: Final Report, DHEW-NIE Grant HEW:NE-G-00-3-0074. Albuquerque, University of New Mexico, Aug 1975
- Shuberg J, Cropley AJ: Verbal regulation of behavior and IQ in Canadian Indian and white children. Developmental Psychol 1972; 7:295-301
- Witelson SF: Developmental dyslexia: two right hemispheres and none left. Science 1971; 195:309–311
- 62. Berry JW: Ecology and socialization as factors in figural assimilation and the resolution of binocular rivalry. Int J Psychol 1969; 4:270–280
- Bruneau OJ: Comparison of behavioral characteristics and self concepts of American Indian and Caucasian preschoolers. Psychol Rep 1984; 54:571-574
- 64. Anderson FN: A mental hygiene survey of problem Indian children in Oklahoma. Ment Hygiene 1936; 20:472-476
- Report of the Council on Exceptional Children to the Bureau of Indian Affairs and the Office of Special Education and Rehabilitation. Washington, DC, Bureau of Indian Affairs, 1978
- Roach RE, Rosecrans CJ: Verbal deficit in children with hearing loss. Except Child 1972; 1:395–399
- 67. Kaplan GJ, Flasman JK, Bender TR, et al: Long term effects of otitis media: a ten year cohort study of Alaskan Eskimo children. Pediatrics 1973; 52:577–585
- 68. Berlin R, Berlin IN: Parents' advocate role in education as primary prevention, in Advocacy for Child Mental Health. Edited by Berlin IN. New York, Brunner/Mazel, 1986
- Caldwell BM: What does research tell us about day care? Child Today 1972; 1:1–4
- Berlin IN: Prevention of emotional problems among Native-American children: overview of developmental issues, in Annual Progress in Child Psychiatry and Child Development. Edited by Chess S, Thomas A. New York, Brunner/Mazel, 1983

# Use of Caffeine to Lengthen Seizures in ECT

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During a course of ECT, seizure duration may become too brief for clinical benefit. Use of higher-energy stimuli may lengthen seizures but may also increase the risk of toxicity, and it is not possible when maximum settings are reached. The authors present the cases of six drug-free depressed inpatients whose seizure durations in ECT declined despite maximum settings on three different ECT devices. In all cases, pretreatment with caffeine lengthened seizures (mean increase=107%), and clinical improvement followed. Caffeine was well tolerated, even in patients with cardiovascular diseases.

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A decline in seizure duration during a course of ECT is common and may result in brief or missed seizures and limited clinical benefit (1-4). The typical clinical approach to avoiding these brief seizures (defined somewhat arbitrarily as 25 seconds or less) (2, 3) is to increase the electrical energy of the ECT stimulus (2). A higher-energy stimulus may produce more encephalopathic side effects, however (1, 5), and is not an option when the ECT device is already at maximum settings.

Shapira et al. (6) reported that intravenous caffeine pretreatment increased ECT seizure duration in a

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patient with a history of nonresponse to ECT. Subsequently, we administered intravenous caffeine to six depressed inpatients receiving ECT whose seizure durations were declining despite maximum settings on three different commercially available ECT instruments. In each case, the use of caffeine resulted in a marked lengthening of the seizure and all patients experienced a clinical remission of their depression.

# **METHOD**

All of the patients in the cases we shall describe were inpatients with a *DSM-III* diagnosis of major depression who had been referred for ECT. Before beginning ECT, each patient was carefully evaluated for general medical and neurological disease, and all psychotropic medications were discontinued. Doses of medications for systemic illness (e.g., antihypertensives, antiarrhythmics) were held constant throughout the course of ECT

The ECT technique was similar for all patients. ECT was administered three mornings a week-Monday, Wednesday, and Friday-in a special ECT suite. Patients received anticholinergic premedication with glycopyrrolate, 0.002 mg/lb. i.m., at least 30 minutes before ECT. Anesthesia was induced with methohexital sodium, 1 mg/kg i.v., followed by succinylcholine, 1 mg/kg i.v., to produce subtotal neuromuscular blockade. All patients were given 100% oxygen by mask, and once they were apneic, their respirations were maintained at 20-25 per minute with positive pressure ventilation by bag. Blood pressure, pulse, and respiratory rate were measured immediately before administration of the anesthetic (baseline) and then at 30, 60, 180, and 300 seconds after the ECT stimulus. For each interval the rate-pressure product, the product of pulse and systolic blood pressure, was calculated to provide an index of myocardial oxygen consumption (work load) (7). The largest product during the 5-minute interval was taken as the maximum rate-pressure product. All patients were monitored with ECG and one-channel EEG.

Choice of stimulus electrode placement was made by the attending physician. For unilateral nondominant ECT, the D'Elia placement (8) technique was used.

The ECT stimulus was administered initially by one of two brief-pulse devices: the MECTA Model C (N=5) or the Thymatron (N=1). These devices deliver a maximum energy output of 59.1 J and 99.8 J, respectively, at a typical impedance of 220  $\Omega$ . Starting stimulus settings for each of the devices were chosen empirically to elicit seizures of 30–100 seconds (2). In order to allow for the delivery of greater stimulus energy during the course of therapy, one patient was switched from the MECTA C to the Thymatron and one patient from the MECTA C to the Medcraft B-24 device (the latter delivers a sine wave stimulus with a maximum energy output of 131.4 J).

For each ECT treatment, seizure duration was determined from the one-channel EEG according to standard criteria (2). If a seizure of less than 30 seconds occurred, the stimulus settings were increased one or two increments (10%–25%) and the patient was restimulated within 30–60 seconds of termination of the previous seizure. No more than two restimulations were administered during any one treatment session. If a single stimulation at maximum settings on a given device elicited a seizure of less than 30 seconds, double sequential stimulation (i.e., immediate restimulation) at the maximum settings was occasionally used. Any prolonged seizure of more than 200 seconds (9) was terminated with methohexital sodium administered intravenously.

When brief seizures (less than 30 seconds) or a considerable, progressive decline in seizure duration occurred after stimulation with maximum machine settings, a trial of intravenous caffeine sodium benzoate was given at the next ECT session. A starting dose of 500 mg of caffeine was chosen on the basis of the report of Shapira et al. (6). After baseline vital signs were obtained, caffeine was administered by means of an intravenous push over 60 seconds. Vital signs were obtained again 2 minutes after the caffeine infusion was completed; during this interval, patients were also observed for evidence of psychomotor agitation and questioned regarding any symptoms of anxiety or dysphoria. The anesthesia, muscle relaxant, and oxygen were then administered as we have described. The delivery of the electrical stimulus occurred 5 minutes after completion of the caffeine infusion.

# CASE REPORTS

Case 1. Mr. A, a 56-year-old right-handed man with recurrent major depression according to DSM-III criteria, had been unresponsive to drug therapy. His active medical illnesses included coronary artery disease with a myocardial infarction 11 months previously, hypertension, insulin-dependent diabetes mellitus, and chronic alcohol abuse. His

medications at the time of ECT included nifedipine, atenolol, digoxin, sublingual nitroglycerin, and isophane (NPH) insulin

Mr. A was started on a series of pulse (MECTA C) unilateral ECTs (figure 1, case 1), but at each ECT he required restimulation at higher energy settings because of brief seizures. By ECT 4, the machine was on maximum settings and the seizure duration was only 32 seconds. At ECT 5, he was switched to the Medcraft device to allow for delivery of greater stimulus energy. By ECT 7, there had been little clinical improvement, so a switch to bilateral ECT was made. Over the next several ECTs, Mr. A continued to have relatively short seizures, despite maximum machine settings and double sequential stimulations. He remained depressed and began to complain of memory disturbances; he was noted to be more confused after each ECT. At ECT 13, caffeine, 500 mg i.v., was administered, which resulted in a 108% increase in seizure duration. The caffeine was well tolerated and was not associated with any complaints of anxiety or change in mood during the infusion. The maximum rate-pressure product for the ECT with caffeine was 29,484; it was 20,020 for the preceding (12th) ECT session. The use of caffeine was not associated with any major cardiac complaints or ECG changes during the course of therapy. At ECT 14, a placebo (4 cc of normal saline) was substituted for caffeine, and the seizure duration fell to 35 seconds. By the time of this treatment, Mr. A evidenced marked confusion and had complaints of memory disturbance, and the ECT was discontinued. Over the next several days, the delirium cleared and the patient's depression was much improved.

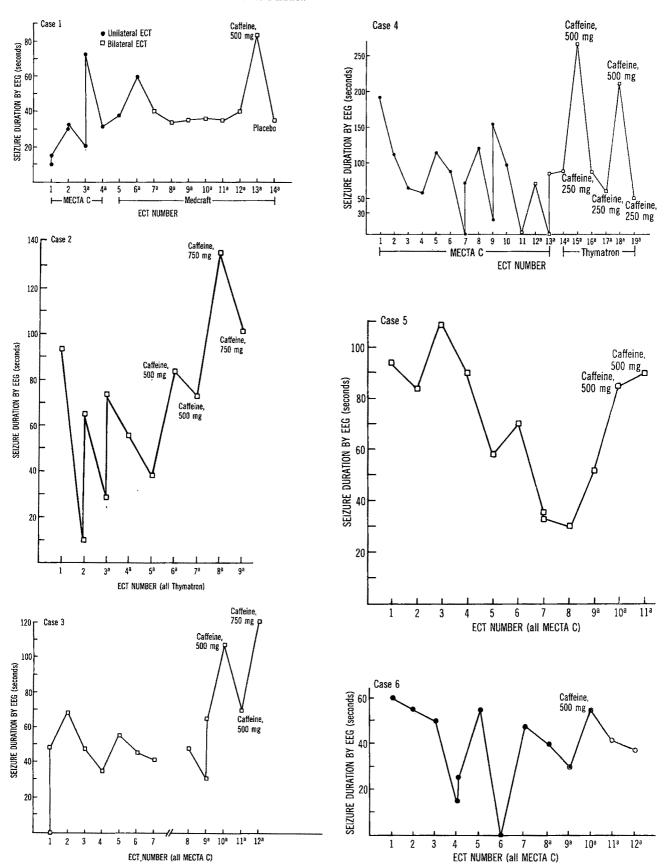
Case 2. Ms. B, a 70-year-old right-handed woman, had a 45-year history of recurrent depressive episodes and DSM-III major depression with psychotic features of 3 months' duration. She had not responded to drug therapy. Her active medical illnesses included hypertension, subcortical arteriosclerotic encephalopathy (10), tardive dyskinesia, and glaucoma. Her medications during ECT included atenolol, pilocarpine, and timolol ophthalmic drops.

A course of bilateral pulse ECT (figure 1, case 2) with the Thymatron device was initiated, but by ECT 3, Ms. B required maximum stimulation (100%) to elicit seizure durations of at least 30 seconds. Seizure duration continued to decline, however, until ECT 6, when caffeine, 500 mg i.v., produced a 121% increase in seizure length. The same dose of caffeine produced a somewhat shorter seizure at the next ECT. Therefore, at ECT 8, the dose of caffeine was increased to 750 mg, resulting in a further 83% increase in seizure length. This dose was repeated at the final ECT, with a modest decline in seizure duration.

Ms. B had an excellent clinical response to the course of ECT; she complained of mild short-term memory disturbance but showed no evidence of prolonged confusion from any of the ECTs. She tolerated the caffeine without any complaints of anxiety or dysphoric mood. The maximum rate-pressure product occurred at ECT 8, when caffeine, 750 mg, produced a rate-pressure product of 17,100. For the other three ECTs with caffeine, the maximum rate-pressure products were no different from those obtained without caffeine. At no time were any of the caffeine-ECT treatments complicated by clinically significant cardiac complaints or ECG changes.

Case 3. Ms. C, a 57-year-old right-handed woman with a 10-year history of recurrent psychotic depression, was re-

# FIGURE 1. Effect of Caffeine on ECT-Induced Seizure Duration



<sup>&</sup>lt;sup>a</sup>Indicates ECT treatment at which maximum energy setting was used.

ferred for ECT with a *DSM-III* diagnosis of major depression with psychotic features of 3 months' duration. Her active medical problems included angina, hypertension, arteriosclerotic encephalopathy, and tardive dyskinesia. Her medications during ECT included triamterene/hydrochlorothiazide, nitroglycerin paste, and diltiazem.

Ms. C received an initial trial of seven pulse (MECTA C) bilateral ECTs (figure 1, case 3). Despite an excellent clinical response, she had a rapid relapse while still hospitalized, which necessitated resumption of the ECT series 3 weeks later. By ECT 9, a progressive decline in seizure duration required restimulation at maximum machine settings. Caffeine, 500 mg i.v., produced a 66% increase in seizure duration at ECT 10, but this effect was lost at ECT 11. The dose of caffeine was therefore increased to 750 mg at ECT 12, which resulted in a 71% increase in seizure duration. At this time, Ms. C was clinically euthymic; she showed no evidence of prolonged confusion but did complain of mild memory disturbance.

The caffeine-ECT treatments were not associated with any complaints of anxiety or dysphoric mood. The maximum rate-pressure product for the ECT before caffeine was given (ECT 9) was 17,270. The maximum rate-pressure products were 17,612 and 21,971 at a caffeine dose of 500 mg; at a dose of 750 mg, the rate-pressure product increased to 26,920.

Case 4. Mr. D was a 79-year-old man with dementia and a 3-month history of DSM-III major depression with melancholia that was unresponsive to drug therapy. Mr. D had had a previous left hemispheric infarction with no residual neurologic deficits, as well as osteopenia and degenerative joint disease of the vertebral column, with a previous spinal fusion. His only medication was acetaminophen.

Mr. D was started on a series of pulse (MECTA C) unilateral ECTs (figure 1, case 4). When he showed inadequate clinical improvement after 10 treatments, a switch to bilateral treatment was made for the rest of the series. Despite two restimulations at successively higher settings, he did not have a seizure in treatment 11. Maximum settings on the MECTA C were used successfully for ECT 12, but they failed to produce any seizure in ECT 13. At this point, he was switched to the Thymatron at 100% to allow for the delivery of greater stimulus energy. The result was a seizure of 83 seconds; these same maximum settings were used for the remainder of the treatment series. At this point, Mr. D remained depressed and showed confusion and impairment of recent memory. At treatment 15, caffeine, 500 mg i.v., was administered, which resulted in a 200% increase in seizure duration; this was terminated by 35 mg i.v. of methohexital sodium. To avoid additional prolonged seizures, the dose of caffeine was reduced to 250 mg at ECT 16 and ECT 17. The apparent dependency of seizure duration on dose was confirmed at ECT 18, when 500 mg of caffeine produced a seizure of 205 seconds, and at ECT 19, when 250 mg of caffeine produced a seizure of 50 seconds. At this point, Mr. D was no longer depressed, and ECT was

The ECTs with caffeine were not associated with anxiety or dysphoria, and there were no significant cardiac symptoms or ECG changes. The ECTs with caffeine were not associated with increases in blood pressure or pulse (maximum rate-pressure product=35,850 at 30 seconds after stimulation) compared to the ECTs before caffeine (maximum rate-pressure product=35,649 at 30 seconds after stimulation).

Case 5. Ms. E, a 72-year-old woman, had a 6-month history of leg and low back pain and a DSM-III diagnosis of major depression, which had been unresponsive to drug therapy. In addition, she had a history of hypertension, migraine headaches, osteoporosis, and osteoarthritis. Her medications at the time of ECT included chlorthalidone, atenolol, piroxicam, potassium chloride, L-tryptophan, and aspirin.

Ms. E started a series of pulse (MECTA C) bilateral ECTs (figure 1, case 5) and had adequate seizure durations until treatment 7, when restimulation at higher settings was needed. Seizure durations continued to decline, and for ECT 9, maximum settings were used. Because of an anticipated continued decline in seizure duration at ECT 10, caffeine, 500 mg i.v., was administered, which resulted in an 82% increase in seizure duration. Ms. E made a full clinical recovery without evidence of prolonged confusion or complaints of memory impairment.

Caffeine sessions were well tolerated and were not associated with any complaints of anxiety or dysphoria. There were no cardiac complaints or major ECG changes. In the first caffeine-ECT session, there was a maximum rate-pressure product of 14,091; in the previous ECT session it was 12,648.

Case 6. Mr. F, a 70-year-old man with clinical evidence of dementia, was referred for ECT for treatment of *DSM-III* major depression with psychotic features, which had been unresponsive to drug therapy. He was receiving coumadin for thrombophlebitis.

Mr. F was started on a series of pulse (MECTA C) unilateral ECTs (figure 1, case 6) and initially had a pattern of declining seizure durations. The sixth ECT produced no seizure. Stimulus settings were increased, and the maximum settings were in use by ECT 8. On ECT 9, despite an immediate restimulation at maximum settings, seizure duration was only 30 seconds according to EEG. Mr. F had shown signs of memory impairment and prolonged confusion by this point and only a partial improvement in his depression. At ECT 10, caffeine, 500 mg i.v., was administered, resulting in an 83% increase in seizure duration. On ECTs 11 and 12, immediate restimulation at maximum settings was used instead of caffeine, but this resulted in seizure durations of only 41 and 37 seconds, respectively. Mr. F was clinically improved, and ECT was discontinued. The prolonged confusion and memory impairment resolved over the next week.

The caffeine was well tolerated, with no complaints of anxiety or dysphoria. There were no cardiac symptoms or significant ECG changes; maximum rate-pressure products were not obtained.

#### **DISCUSSION**

A decline in seizure duration during a course of ECT is common (4) and was seen in all six of our cases. When faced with brief seizures at maximum machine settings, the clinician has a limited number of options. Drugs that have anticonvulsant properties (e.g., benzodiazepines) or that shorten seizure duration (e.g., lidocaine, L-tryptophan) should be discontinued (11, 12). Since the anesthetic methohexital sodium also has anticonvulsant properties, a lower dose or a switch to

a nonbarbiturate anesthetic such as ketamine may prolong seizure duration (14). However, ketamine is associated with a higher risk of developing an emergent delirium and/or dissociative psychological states (13). Hyperventilation and hyperoxygenation can also be used to prolong seizure duration (14). In the present series of patients, care was taken to provide uniform respiratory assistance across all ECTs so as to minimize the confounding effects of such variables. The convulsant agent pentylenetetrazole (15) was once used as an adjunct to ECT but is no longer commercially available.

A switch to a higher-energy machine, if available, may be only transiently effective in lengthening seizure duration, as shown in cases 1 and 4. It should be noted that the latest models of pulse ECT devices by MECTA (SR and JR), Medcraft (B-25), and Somatics (Thymatron) are all equivalent in terms of maximum energy output. The use of immediate double stimulations at maximum machine settings also may not be effective, as shown in cases 1 and 6. Both of these latter options involve the delivery of greater stimulus energy and, potentially, an increased risk of CNS toxicity (1, 5), a factor that may have been involved in cases 1, 4, and 6.

In our six patients, seizure duration had declined during a course of ECT despite maximum machine settings and, in cases 1 and 6, double sequential stimulation. In each case, pretreatment with intravenous caffeine resulted in lengthening of the seizure by an average of 107% over that of the preceding ECT session. While formal ratings of mood were not performed in this preliminary series of observations, clinical improvement was achieved in each case.

All patients tolerated the caffeine pretreatment without major side effects. Although caffeine has anxiogenic effects in some patients (16), there were no complaints of anxiety or dysphoric mood changes during or after intravenous infusion of caffeine in our patients. Vital signs taken during ECT showed the expected blood pressure and pulse rise, with a return to baseline within 5-10 minutes. Although the mean increase in rate-pressure product over baseline sessions for the first caffeine-ECT session was only 7%, some patients did show increases with caffeine. Nevertheless, there were no complaints of chest pain or palpitations, even in those patients with preexisting angina and/or hypertension. Cardiac arrhythmias were not observed. Seizure duration with caffeine showed a mean increase of 107%. In case 4, the initial use of 500 mg of caffeine resulted in a seizure of 250 seconds, which was terminated by intravenous methohexital sodium. In this context, a high serum level of theophylline (like caffeine, a methylxanthine) has been linked to the occurrence of status epilepticus during ECT (17). A prolonged seizure (9) may theoretically increase the risk of transient encephalopathic changes, with prolonged confusion and/or increased agitation in the postictal period. Despite increases in seizure duration in all of our patients when caffeine was administered,

however, nurses' assessments of reorientation intervals after ECT revealed no evidence of prolonged confusion. In summary, our six patients tolerated pretreatment with caffeine well. Still, further experience with a larger number of patients is needed to fully determine the risks associated with intravenous caffeine as a pretreatment in ECT.

The mechanisms of action of caffeine in lengthening seizures in ECT is unknown and was not examined in our clinical observations. Shapira et al. (6) suggested that caffeine may lengthen seizures by inhibition of adenosine at the central A<sub>1</sub> receptor. Caffeine is also a cerebral stimulant, as are other agents that have a potentiating effect on seizure duration (e.g., amphetamine, theophylline, pentylenetetrazole). Whether these agents act on seizure duration through their known monoaminergic effects or whether some other mechanism is involved remains to be demonstrated.

Of interest in our patients was the apparent dose-dependent relationship of the response to caffeine. In all cases in which the dose of caffeine varied, the longest seizure occurred with the highest dose of caffeine. Careful clinical application of this dose-dependent relationship may allow adjustment of seizure duration to the range desired. Further work is also needed to determine the optimal interval between infusion of caffeine and administration of the ECT stimulus. For example, after a brief seizure, can caffeine be given before restimulation to augment the second seizure?

In summary, during a course of ECT, seizure duration may shorten and become inadequate for therapeutic benefit. The standard clinical practice of increasing the stimulus setting to lengthen seizures is obviously not possible when the maximum settings are reached. Pretreatment with intravenous caffeine may prove to be effective in lengthening seizures in such difficult cases.

#### REFERENCES

- Ottosson J-O: Experimental studies on the mode of action of electroconvulsive therapy. Acta Psychiatr Neurol Scand .Suppl) 1960; 145:1–141
- 2. Weiner RD: The psychiatric use of electrically induced seizures. Am J Psychiatry 1979; 136:1507–1517
- Fink M, Johnson L: Monitoring the duration of electroconvulsive therapy seizures. Arch Gen Psychiatry 1982; 39:1189– 1191
- Fink M: Convulsive Therapy: Theory and Practice. New York, Raven Press, 1979
- 5. Fink M, Kahn RL, Green M: Experimental studies of the electroshock process. Dis Nerv Syst 1958; 19:113-118
- Shapira B, Zohar J, Newman M, et al: Potentiation of seizure length and clinical response to electroconvulsive therapy by caffeine pretreatment: a case report. Convulsive Therapy 1985; 1:58-60
- 7. Jones RM: Rate pressure product. Anesthesia 1980; 35:1010–1011
- d'Elia G: Unilateral ECT. Acta Psychiatr Scand (Suppl) 1970; 215:5–98
- Kaufman KR, Finstead BA, Kaufman ER: Status epilepticus following electroconvulsive therapy. Mt Sinai J Med 1986; 53: 119–122

#### NEUROLEPTIC-INDUCED MOVEMENT DISORDERS

- 10. Coffey CE, Hinkle PE, Weiner RD, et al: Electroconvulsive therapy of depression in patients with white matter hypertensity. Biol Psychiatry 1987; 22:629-636
- 11. Standish-Barry HMAS, Deacon V, Snaith RP: The relationship of concurrent benzodiazepine administration to seizure duration in ECT. Acta Psychiatr Scand 1985; 71:269-271
- Price WA, Zimmer B: Effect of L-tryptophan on electroconvulsive therapy seizure time. J Nerv Ment Dis 1985; 173:636– 638
- Guerra F: Ketamine may exacerbate psychiatric illness. Anesthesiology 1980; 53:177-178
- Bergsholm P, Gran L, Bleie H: Seizure duration in unilateral electroconvulsive therapy. Acta Psychiatr Scand 1984; 69:121– 128
- Thigpen CH, Cleckley HM: Electroconvulsive therapy with enhancement by pentylenetetrazol. Am J Social Psychiatry 1984; 4:25-27
- Greden JF: Anxiety or caffeinism: a diagnostic dilemma. Am J Psychiatry 1974; 131:1089–1092
- 17. Peters SG, Wochos DN, Peterson GC: Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. Mayo Clin Proc 1984; 59:568–570

# Clinical Nonrecognition of Neuroleptic-Induced Movement Disorders: A Cautionary Study

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Extrapyramidal side effects are a major limitation in the use of neuroleptics, and tardive dyskinesia is a special public health problem. Accurate clinical diagnosis of extrapyramidal syndromes is necessary for effective management. The authors compared clinicians' recognition of the major extrapyramidal syndromes in 48 psychotic inpatients with independent blind diagnoses by clinical researchers using standardized ratings. The major finding was a high rate of clinical underrecognition of all major extrapyramidal syndromes, especially tardive dyskinesia. The authors discuss the clinical predictors of nonrecognition of extrapyramidal side effects and recommend improved training in their detection.

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E xtrapyramidal side effects of neuroleptics (dystonia, akathisia, akinesia, parkinsonism, and tardive dyskinesia) must be promptly recognized to maximize

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compliance (1), decrease iatrogenic complications, and improve the patient's quality of life (2, 3). Effective management of extrapyramidal side effects depends on the ability of clinicians who prescribe neuroleptics to make accurate diagnoses.

Previous anecdotal reports have noted misdiagnosis of dystonia (4) and akathisia (5) and difficulty in distinguishing akinesia from depression (6). There is also evidence that tardive dyskinesia is underreported by patients (7) and that its severity can be underestimated by clinicians (8). Chronic parkinsonian and dyskinetic syndromes secondary to neuroleptic treatment have been misdiagnosed in medical and neurologic clinics (9, 10). Chronic psychiatric patients evaluated in psychiatric clinics have been shown to have a high prevalence of mild tardive dyskinesia but only when diagnosed by expert raters (11).

Although this anecdotal evidence suggests major clinical problems in the accurate diagnosis of neuro-leptic-induced extrapyramidal side effects, to our knowledge only one study (12) has systematically evaluated discrepancies between research and clinician diagnoses of tardive dyskinesia. The purpose of our study was to assess prospectively the level of detection of extrapyramidal syndromes achieved by the attending psychiatrists and psychiatric residents routinely managing psychotic patients in the acute inpatient psychiatric units of a university medical center. The results help to explain discrepancies in the rates of extrapyramidal side effects between clinical and re-

search studies and have serious implications for clinical practice and training.

#### **METHOD**

We studied 58 patients who had been consecutively admitted to the three acute inpatient units of Payne Whitney Psychiatric Clinic and who met the study criterion of having an acute psychosis without a known organic mental syndrome. Within 48 hours of admission and then weekly until discharge, each patient was rated by at least one researcher (P.J.W. or J.J.M.) who was blind to the clinician's diagnosis or treatment of extrapyramidal syndromes. All clinical staff were kept blind to the purpose of the study.

# Ratings of Extrapyramidal Symptoms

The presence and severity of parkinsonism, akinesia, akathisia, dystonia, and tardive dyskinesia were determined by the researchers with modifications of the Webster Parkinson's disease scale (13), the akinesia scale of Rifkin et al. (14), the Van Putten akathisia scale (15), the Extrapyramidal Symptom Rating Scale (16), and the Abnormal Involuntary Movement Scale (AIMS) (17).

The research diagnosis of tardive dyskinesia was based on an AIMS global score of 2 or higher and was confirmed by independent assessment by a second rater. For parkinsonism, akinesia, and akathisia, the research diagnosis was based on a rating of 2 or higher on a 4-point global scale, which corresponds clinically to a range of mild (but unequivocal) to severe symptoms. Dystonia was assessed by means of the Extrapyramidal Symptom Rating Scale, which determines either its presence or absence, and patient reports of a history of dystonia.

The clinicians' diagnoses of extrapyramidal side effects were established through chart review (by P.J.W.) after each patient's discharge. The results of the physical examination at admission, emergent physical findings, the patient's complaints, nurses' observations, recorded quotations and handwriting samples from the patient, family comments, and the physician's differential diagnosis of changes in the patient's behavior consistent with neuroleptic-induced extrapyramidal side effects were reviewed systematically. Medication histories (neuroleptic doses and dose changes, anticholinergic or other treatments, and "p.r.n." treatments for extrapyramidal side effects) were recorded. Clinical observations of extrapyramidal symptoms derived from the chart over the hospital course were contrasted with the patient's research ratings.

The following operational criteria for clinician nonrecognition of extrapyramidal side effects were chosen to standardize the assessment of clinical diagnostic accuracy: 1) nonrecognition by the physician of persistent dyskinesia of mild or greater severity, 2) failure to recognize acute dystonia when its symptoms

were observed by staff or reported by the patient, 3) failure to document moderate rigidity or tremor within 1 week of detection by research assessment, 4; physician's failure to consider akinesia or akathisia as a diagnostic possibility within 1 week of onset of typical behavioral or motoric symptoms.

# Characteristics of Unit Staff and Patients

The staff on each of the 24-bed units included two full-time supervising attending psychiatrists, four psychiatry residents in postgraduate year 2, and one inpatient chief resident in postgraduate year 4. The data were collected between August and October, the second through fourth months of the residents' second-year inpatient experience. The residents had also completed 5 months of psychiatric training during their internships and a course on the inpatient treatment of acute psychosis. All trainees had at least two attending supervisors who periodically examined all of their patients.

Of the 58 patients examined, 48 received at least 1 week of continuous neuroleptic treatment and completed at least two research ratings of extrapyramidal side effects. These 48 patients were relatively young (mean±SD age=27.4±16.9 years) and consisted of 29 females and 19 males. Their DSM-III diagnoses at discharge included schizophrenia (N=19), schizoaffective disorder (N=12), schizophreniform disorder (N=3), bipolar disorder, manic or mixed (N=9), and major depression with psychotic features (N=5). Their mean±SD length of stay was 28.0±14.6 days, and they received  $3.6\pm1.7$  research ratings. The average dose of neuroleptics during acute treatment was 1401±1064 mg/day of chlorpromazine equivalents, and the range was 200-5000 mg/day. Initial anticholinergic prophylaxis was begun for 29 patients (60%), and eventually 44 patients (92%) received adjuvant anticholinergic therapy. Of note in the clinical management of this group are the relatively high neuroleptic doses used and the high frequency of administration of anticholinergic agents.

The number of patients in whom extrapyramidal side effects were identified by means of the standard research assessments was high. Of the 48 patients, 29 developed parkinsonian signs, 23 had akinesia (all of these patients had coexisting parkinsonian signs), 27 had akathisia, three had dystonic reactions during research examinations, and 11 had dystonias according to the combination of clinical diagnosis and research dystonia history. Ten patients (out of the original 58) had tardive dyskinesia.

#### **RESULTS**

Each patient who had extrapyramidal side effects according to the researcher's diagnosis was categorized in terms of presence or absence of an accurate clinical diagnosis. Table 1 reveals striking and highly signifi-

TABLE 1. Research and Clinical Diagnoses of Neuroleptic-Induced Extrapyramidal Syndromes in 48 Psychotic Patients

Extrapyramidal Syndrome	Patients Given Research Diagnosis	Cli	nical Diagnosis	McNemar Test of Difference Betweer Clinician and Researcher Errors		
		Patients Given Diagnosis	Percent of Patients Given Research Diagnosis	$\chi^2$ (df=1)	p	
Dystonia	3	1	33		<del></del>	
Parkinsonism	29	17	59	10.08	<.005	
Akinesia	23	14	61	7.11	<.01	
Akathisia Tardive	27	7	26	18.05	<.001	
dyskinesia <sup>a</sup>	10	1	10	7.11	<.01	

<sup>&</sup>lt;sup>a</sup>Total sample included 58 patients.

TABLE 2. Global Severity of Extrapyramidal Syndromes in Cases Recognized and Unrecognized by Clinicians

Extrapyramidal Syndrome	Recognized by Clinician		Unrecognized by Clinician <sup>a</sup>						
		Severity Rating			Severity Rating		Comparison of Ratings		
	Patients	Mean	SD	Patients	Mean	SD	t	df	р
Parkinsonism	17	2.38	0.59	12	2.60	0.53	1.05	27	n.s.
Akinesia	14	2.70	0.80	9	3.17	0.50	1.73	21	<.05
Akathisia	7	3.14	0.64	20	2.40	0.72	2.54	25	<.05
Tardive dyskinesia									
Global	4	2.50	0.58	6	2.33	0.51	0.47	8	n.s.
Oral	4	2.75	0.50	6	1.50	1.00	2.60	8	<.05
Extremity	4	1.50	1.29	6	2.33	0.52	1.22	8	n.s.
Extremity/facial <sup>b</sup>	4	0.24	0.36	6	1.09	0.64	2.77	8	<.05

<sup>&</sup>lt;sup>a</sup>See text for definition of undiagnosed cases.

cant rates of disagreement between the research and clinical diagnoses across all types of extrapyramidal side effects. Except for three cases of dystonia, all the cases of extrapyramidal side effects documented by the clinical method were picked up by the research method, but many cases were missed by the clinicians but detected by the research assessment. There was no significant difference between the patients whose extrapyramidal side effects were and were not recognized clinically in terms of demographic characteristics, discharge diagnoses, rates of anticholinergic prophylaxis, or (except for akathisia) neuroleptic doses.

Only one of the 10 patients with tardive dyskinesia was accurately diagnosed by the clinicians. Among the nine patients with undiagnosed cases, three had nurse or physician notes that mentioned abnormal dyskinetic movements but no follow-up diagnosis of tardive dyskinesia. Considering these three cases as recognized cases of tardive dyskinesia allows a comparison of four "recognized" and six unrecognized cases. Overall severity on the global AIMS did not differentiate the patients with recognized and unrecognized cases (see table 2). However, oral movements were significantly more severe in the patients with recognized tardive dyskinesia, whereas the patients with unrecognized cases had a predominance of extremity movements.

Mild parkinsonism (tremor, rigidity, micrographia, or decreased fine motor coordination) was found by the researchers in 29 patients. Rigidity was the most severe clinical sign in 26 of them. In 17 cases the

parkinsonism was accurately diagnosed by the clinician. Of the 12 cases that were inaccurately diagnosed, eight were missed completely, two were identified with a delay of more than 1 week, and two were underrated in global severity. The mean researcher ratings of global severity for the unrecognized and recognized cases of parkinsonism did not significantly differ (table 2), suggesting that overall clinical severity did not determine nonrecognition.

Of the 23 researcher-diagnosed cases of akinesia, 14 were accurately identified by clinicians. Among the nine missed cases, five had no diagnosis or no mention of the differential diagnosis of akinesia, three received the likely misdiagnosis of "depression" (without consideration of the possibility of akinesia despite the temporal correlation of akinesia with neuroleptic administration), and one was severe but was rated by clinical staff as "mild" and received no treatment. Severity of symptoms predicted clinical diagnostic accuracy but in an unexpected direction. The cases missed by the clinicians had significantly more severe symptoms than the recognized cases (table 2). Patients with misdiagnosed akinesia were also significantly more likely to suffer from coexisting akathisia (t=3.8, df=21, p<.001).

The clinical staff inaccurately diagnosed 20 of the 27 researcher-diagnosed cases of akathisia. The clinical errors consisted of nine cases in which the akathisia went unnoticed, seven cases of errors in the differential diagnosis of agitation/restlessness/"acting out" after

<sup>&</sup>lt;sup>b</sup>Sum of the AIMS extremity movement items divided by the sum of the AIMS facial and oral movement items.

recent increases in neuroleptic dose, and four cases of delay in diagnosis of more than 1 week. Underrecognition of akathisia was significantly associated with lower severity research ratings, suggesting that milder (or less reliably ratable) forms of akathisia are missed in clinicians' assessments. In addition, the patients with unrecognized akathisia received higher neuroleptic doses than the patients with diagnosed akathisia (mean±SD=1700±955 versus 1007±406 mg/day of chlorpromazine equivalents; t=2.6, df=25, p<.01). The patients with undiagnosed akathisia also suffered from more severe coexisting akinesia than those with accurate akathisia diagnoses (t=2.8, df=25, p<.05).

Acute dystonic reactions were difficult to assess accurately on the basis of patient reports because of the patients' poor recall and unreliable descriptions of dystonias. Chart review revealed three cases of dystonias missed by systematic research assessment with the Extrapyramidal Symptom Rating Scale. In contrast, however, three patients had acute dystonias during research examinations (two had oculogyric crises and one had neck torticollis); all occurred early in the course of neuroleptic treatment. In all three cases, the patients complained of their symptoms to the nursing staff. Two were misdiagnosed: one was described as "psychotic behavior" by the physician on call, and the other was considered "hysteric" by the nursing staff and received no physician evaluation. No treatment was given to either patient.

Each patient (N=16) who gave a preadmission history of distressing acute extrapyramidal side effects during previous neuroleptic exposure received anticholinergic prophylaxis. However, presence or absence of anticholinergic prophylaxis was not a predictor of subsequent physician nonrecognition of extrapyramidal syndromes. Every case of acute extrapyramidal side effects that was clinically diagnosed was initially treated with adjuvant medication, never with a reduction of neuroleptic dose.

### **DISCUSSION**

The major finding of this study was a high rate of clinician nonrecognition of extrapyramidal side effects. This finding suggests that wide differences in the frequency of extrapyramidal side effects across studies may be partly due to variations in the expertise and sensitivity of the examiners. These results definitely point to severe limitations in using chart review alone in quality assurance studies to determine the nature and extent of extrapyramidal side effects. Most important clinically, however, are the serious yet correctable blind spots in the clinical diagnosis of extrapyramidal side effects. We wish to emphasize that there was nothing difficult about the research evaluation of extrapyramidal symptoms and that clinical nonrecognition of extrapyramidal side effects can be reduced with better training and systematic attention to this problem.

Tardive dyskinesia, despite its persistent nature, is often missed, especially when its symptoms involve the extremities rather than the "classic" orobuccal areas. This selective nonrecognition of extremity dyskinesias may arise for several reasons: this form of tardive dyskinesia is less well known to clinicians, patients may disguise their hand dyskinesias better than oral ones, hand dyskinesias often occur only when the patient is walking, shoes usually are not removed during examinations, and hand choreas may be mistaken for tremors. Physicians should inspect the extremities for choreiform movements and generally have a high index of suspicion for any form of tardive dyskinesia in any patient receiving antipsychotic medications.

Severe forms of akinesia tend to be more frequently underrecognized than milder cases. This may be because severely akinetic patients complain less about their symptoms than patients with milder cases or because severe akinesia is more likely to be misdiagnosed as depression. Akinesia should be considered in the differential diagnosis of any patient taking neuroleptics who becomes amotivational, depressed, lethargic, or slowed down. Staff cannot expect the patient to report these changes spontaneously.

The higher neuroleptic doses found in the patients with unrecognized akathisia than in those with recognized akathisia may reflect the eventual appropriate lowering of neuroleptic dose when the akathisia was diagnosed. For those patients whose akathisia is misdiagnosed as agitation or psychosis, the neuroleptic dose will instead be increased. Akathisia also seemed to be missed when it presented behaviorally (i.c., as an elopement or incident requiring seclusion) or when the patient was too psychotic, disorganized, or akinetic to complain of akathisia. In the very psychotic patient, the subjective experience of akathisia can only be assessed (if at all) by a direct, focused patient interview. In fact, akathisia should be considered for any restlessness, agitation, or acting-out behavior of recent onset that temporally coincides with escalating neuroleptic dose, even if the patient does not voluntarily mention severe inner restlessness. The clinician should not rule out akathisia until completing such a focused, active inquiry for subjective restlessness and/or behavioral agitation.

Dystonia was the only extrapyramidal side effect missed by research rating but not clinical diagnosis, suggesting that dystonias cannot be accurately ascertained by interview alone. The intermittent nature of dystonias usually requires that an assessment be made by means of patient history rather than physical examination. Unfortunately, the historical method for diagnosing dystonias proved to be unreliable. Even more discouraging was what happened with the acute dystonias actually observed by both researchers and staff. Despite the small number of such cases, an unequivocal rate of 67% for the misdiagnosis of typical and classic dystonias is noteworthy, and it seems that textbook cases of acute dystonia are still

frequently attributed to psychopathology. The dystonias in our study seemed to be missed because they occurred shortly after admission, when the staff did not know the patients, some of whom were very psychotic. Other immediate management issues seemed to preempt the careful observation necessary to make a diagnosis of dystonia. We therefore recommend that all inpatient staff automatically consider any new muscle spasm or posturing arising early in neuroleptic treatment to be a dystonic reaction.

Other useful diagnostic techniques include a focused clinical interview with repeated attempts to elicit complaints of all subtypes of extrapyramidal side effects, interviewing family members about the patient's current behavior and whether it coincides with extrapyramidal side effects in the past, and being cautious about any report or past history of "hysterical" or "psychotic" abnormal movements. Another helpful technique is a review of the timing and doses of all medications administered to find pharmacologic correlates with the undiagnosed behavior. Graphing the medication record alongside recorded observations of the patient's symptoms can highlight medication-induced toxicity patterns.

The clinicians in this study consistently provided anticholinergic prophylaxis for patients who gave prior histories of extrapyramidal side effects. They also promptly treated diagnosed extrapyramidal symptoms with adjuvant medication. However, it is striking that neuroleptic dose reduction was never the initial treatment when such a symptom was recognized. It seems that lowering the neuroleptic dose should have been used more often. In addition, using prophylactic anticholinergic agents did not improve the recognition rate. Therefore, clinicians should not be lulled into a false sense of security by the belief that anticholinergic prophylaxis solves the problems of accurately assessing extrapyramidal side effects.

This study of clinician versus research diagnosis of extrapyramidal symptoms has several limitations. The clinician diagnoses were determined by means of retrospective chart review, which depends on accurate chart documentation and may have underestimated the rates of actual clinician diagnoses of extrapyramidal side effects. This retrospective method was chosen to avoid alerting the clinicians to the nature of the study. However, since the necessity for documenting extrapyramidal side effects is carefully emphasized at our institution and the charts are well documented in other ways, it seems unlikely that a diagnosis of an extrapyramidal syndrome would not have become part of the treatment record.

Another potential methodologic problem of this study is the lack of research rater blindness to the purpose of the study. This may have inflated the number of research diagnoses of extrapyramidal side effects, resulting in an artificially high rate of clinical nonrecognition. However, the rates of clinical nonrecognition across all subtypes of extrapyramidal symptoms (except akathisia) did not proportionately

decrease as the researcher-rated severity increased. It was not just subtle extrapyramidal effects that were not recognized, but unequivocal ones as well. Weekly movement disorder research rounds served as reliability checks of the primary raters (P.J.W. and J.J.M.). Therefore, we feel researcher bias does not explain these results.

Another concern is that there is a high degree of intrinsic overlap in the presentations of certain extrapyramidal side effects and primary psychiatric diagnoses and that the research rater may have mistaken primary psychopathology for extrapyramidal side effects. This is most possible for the research-diagnosed akinesia and akathisia. Although we cannot rule out the possibility that symptom overlap increased the researcher diagnoses of extrapyramidal side effects, the same difficulties face the treating clinical teams, who need to routinely consider akathisia and akinesia in the differential diagnoses of sudden, unexplained behavioral changes (4-6). Indeed, the researchers performing the chart reviews accepted as an accurate clinical diagnosis any documentation that included extrapyramidal side effects as part of the differential diagnosis regardless of the final conclusion. Moreover, seemingly "hard" and unequivocal neurologic findings such as dystonia and dyskinesia were missed at even higher rates than akinesia and akathisia!

Other methodologic questions relate to the relevance and generalizability of these findings to nationwide patterns in the diagnosis of extrapyramidal side effects. It is possible that these results reflect a particular blind spot of the institution where the study was performed. A related issue is the timing of the study, which occurred early in the 12-month training cycle; the results may differ with more experienced residents. We think that this is an inadequate explanation of our findings given that the residents were well qualified and were supervised by full-time attending physicians. Furthermore, a similar chart review conducted at a Veterans Administration teaching hospital (12) also demonstrated a 75% rate of nonrecognition of tardive dyskinesia by clinical staff, strongly suggesting the possibility of a nationwide pattern of nonrecognition of extrapyramidal side effects. We suspect that the underdiagnosis of extrapyramidal side effects reflects the clinical limitations of attending and resident psychiatrists who are not specifically and extensively trained in the evaluation of extrapyramidal symptoms and who do not systematically rate them at regular intervals.

The ability to perform a sophisticated assessment of extrapyramidal side effects is not easily learned and requires specific training. This study underscores the need for careful supervision, training, and attention to the accurate diagnosis of extrapyramidal side effects. It also seems clear that repeated and systematic evaluation of extrapyramidal symptoms with standardized measures (at least every 2 weeks and at admission and discharge) should be made routine on every acute inpatient unit. General psychiatric interviewing meth-

ods and mental status examinations without specific and systematic examinations for extrapyramidal side effects may distract clinicians by providing spurious psychologic explanations for neuroleptic-induced motoric and behavioral changes. Without significant remediation of errors in diagnostic methods and training insufficiencies, it is likely that extrapyramidal side effects will continue to be underdiagnosed at an alarmingly high rate.

### REFERENCES

- 1. Weiden P, Shaw E, Mann JJ: Causes of neuroleptic noncompliance. Psychiatr Annals 1986; 16:571-575
- Kane JM (ed): Drug Maintenance Strategies in Schizophrenia. Washington, DC, American Psychiatric Press, 1984
- Diamond RI: Quality of life: the patient's point of view. J Clin Psychiatry 1985; 46:29–35
- Fahn S: The varied clinical expressions of dystonia. Neurol Clin North Am 1984; 2:541–554
- 5. Van Putten T: The many faces of akathisia. Compr Psychiatry 1975; 16:43-47
- Van Putten T, May PRA: "Akinetic depression" in schizophrenia. Arch Gen Psychiatry 1978; 35:1101–1107
- 7. Alexopoulos GS: Lack of complaints in schizophrenics with

- tardive dyskinesia. J Nerv Ment Dis 1979; 167:125-127
- Rosen AM, Mukherjee S, Olarte S, et al: Perception of tardive dyskinesia in outpatients receiving maintenance neuroleptics. Am J Psychiatry 1982; 139:372-373
- Grimes JD: Drug-induced parkinsonism and tardive dyskinesia in nonpsychotic patients (letter). Can Med Assoc J 1982; 126: 468
- Murdoch PS, Williamson J: A danger in making the diagnosis of Parkinson's disease. Lancet 1982; 1:1213–1214
- Asnis GM, Leopold MA, Duvoisin RC, et al: A survey of tardive dyskinesia in psychiatric outpatients. Am J Psychiatry 1977; 134:1367–1370
- 12. Hansen TE, Casey DE, Weigel RM: TD prevalence: research and clinical differences, in New Research Abstracts, 139th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1986
- 13. Webster DD: Clinical analysis of the disability in Parkinson's disease. Mod Treat 1968; 5:257-282
- Rifkin A, Quitkin F, Klein DF: Akinesia. Arch Gen Psychiatry 1975; 32:672–674
- 15. Van Putten T: Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 1974; 31:61-72
- Chouinard G, Annable L, Ross-Chouinard A, et al: Ethopropazine and benztropine in neuroleptic-induced parkinsonism. J Clin Psychiatry 1979; 40:147–152
- Guy W: ECDÉU Assessment Manual for Psychopharmacology.
   Washington, DC, US Department of Health, Education and Welfare, 1976, pp 534-537

# Deceased Members of the American Psychiatric Association

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# The Prognostic Relevance of Delusions in Depression: A Follow-Up Study

Randy L. Kettering, Ph.D., Martin Harrow, Ph.D., Linda Grossman, Ph.D., and Herbert Y. Meltzer, M.D.

To determine whether delusional depression has a different clinical course from other types of depression, the authors followed up 31 unipolar delusional depressed patients, 28 unipolar nonpsychotic depressed patients, and 51 schizophrenic patients 14 months after hospital discharge. Patients were assessed on 1) overall outcome, 2) psychotic, anxiety-neurotic, and depressive symptoms, 3) social and work functioning, and 4) rehospitalization. The delusional depressed patients showed significantly more mood-incongruent delusions at follow-up. Surprisingly, the nonpsychotic depressed patients exhibited more depressed mood and significantly more anxiety at follow-up. The findings suggest that the diagnostic distinction between delusional and nonpsychotic depression is relevant to the clinical course of major depression.

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The current research was designed to investigate whether depressed inpatients who are delusional have a poorer outcome after hospitalization than depressed inpatients who are not psychotic.

Over the past decade there has been an increased focus on patients who have psychotic or schizophrenic-like symptoms that coexist within an affective syndrome. Delusional depression is a syndrome in which particular psychotic and affective symptoms coexist, and studying this phenomenon is one means of assessing the prognostic and diagnostic importance of delusions in a patient with a full depressive syndrome. A

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question central to the field is whether delusional depression is only a more severe manifestation of an affective disorder or whether it should be considered a disorder with separate and distinct characteristics. It is not yet certain whether depressed patients with delusional symptoms have poorer outcomes after hospital discharge than depressed patients who are not delusional or whether the presence of mood-incongruent delusions in depression suggests either a different kind of disorder or one with a poorer outcome. Researchers (1–3) have begun to investigate this issue.

Delusional depression has been compared to nondelusional depression in terms of biological, genetic, phenomenologic, family background, and treatment response variables, but the significance of the delusional symptoms for demarking a possible different type of disorder is still unclear. Patients with unipolar delusional depression have been reported to have significantly lower levels of serum dopamine β-hydroxylase activity (4) and CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) (5) than nondelusional depressed patients. Delusional depressed patients also have been reported as having a higher prevalence of cortisol nonsuppression after dexamethasone administration. In contrast, delusional depressed patients have been reported as not differing significantly from nonpsychotic depressed patients in the frequency of positive family history of affective disorder or psychiatric disorder (6-8), and a greater history of hospitalization has not been consistent across studies (6-9). A relationship between delusional depression and a high prevalence of bipolar disorder among relatives has been reported (10).

Treatment response has distinguished patients with delusional unipolar depression from those with nondelusional major depression. Recovery without the aid of active treatment intervention is less frequent among delusional depressed patients than among patients with many other types of depressive disorders (8, 9). The clinical response to tricyclic antidepressants may differentiate the two depressive groups (8, 9, 11, 12); delusional depressed patients are less responsive to this form of intervention.

Investigators have noted that these two patient groups differ in the type and severity of symptoms present. Scores on the Hamilton Rating Scale for

Depression (13) were significantly lower among delusional depressed patients (7) even after these scores were controlled for items related to delusional ideation (e.g., guilt, hypochondriasis, depersonalization and derealization, paranoia, and sense of worthlessness). Symptoms such as lack of energy and anxiety have been reported as significantly more prevalent in unipolar nondelusional depressed patients (11), and similar observations have been noted for psychomotor retardation and agitation (7–9), suggesting that the nondelusional depressed patients may exhibit more severe vegetative symptoms.

The significance of psychotic symptoms in the longterm clinical course and posthospitalization outcome of a major affective disorder is as yet unclear. The current research used a variety of outcome indices for delusional and nonpsychotic patients with unipolar major depression to determine the relevance of delusional ideation to the course of illness and to adjustment 14 months after hospital discharge. Specifically, the following questions were addressed:

- 1. Does the presence of delusions in major depressive disorders during hospitalization suggest a poor overall outcome 14 months after hospital discharge?
- 2. Do delusional and nonpsychotic depressed patients differ markedly in the degree or type of symptoms after discharge?
- 3. Is the posthospitalization social or instrumental role performance or the rehospitalization rate of delusional depressed patients more similar to that of non-psychotic depressed patients or that of schizophrenic patients?

#### **METHOD**

# Patient Sample

The subjects were 110 psychiatric inpatients from two major research programs that collaborated to study prospectively dimensions of major psychiatric disorders during hospitalization and then to follow up these patients after hospital discharge.

One group comprised 58 patients from the Mental Health Clinical Research Center program at the Illinois State Psychiatric Institute and the University of Chicago, which is studying biological and psychological factors in major psychotic disorders (4, 14). The other group consisted of 52 patients from the Chicago Follow-Up Study, a longitudinal research program based at Michael Reese Hospital that is investigating thought disorder, psychosis, and adjustment over time in schizophrenic patients and patients with other major psychiatric disorders (15–17).

Follow-up interviewers from the two research programs were trained conjointly. All patients were diagnosed according to the Research Diagnostic Criteria (RDC) (18). The sample included three groups: 31 unipolar delusional depressed patients (17 from the Mental Health Clinical Research Center program and

14 from the Chicago Follow-Up Study), 28 unipolar nonpsychotic depressed patients, and 51 schizophrenic patients. Patients were included in the delusional depressed group if during hospitalization or the 1 month before hospitalization they exhibited full delusional ideation as defined in the RDC. The patient groups did not significantly differ in age, and the overall mean age was 27.5 years (range=19–56 years). The percentage of male subjects was 42% among the delusional depressed patients, 41% among the nonpsychotic depressed patients, and 72% among the schizophrenic patients. The two depressive groups did not differ with respect to sex, although both groups contained larger percentages of women than did the schizophrenic group ( $\chi^2$ =7.9, df=1, p<.006).

A subset of 23 of the depressed patients from the Mental Health Clinical Research Center program was rated on the Hamilton Rating Scale for Depression (13) and the Brief Psychiatric Rating Scale (BPRS) (19) at both hospital admission and discharge. Extensive interviewer training with these scales was conducted as part of the program, and high interrater reliability was obtained. The ratings on the Hamilton scale showed similar degrees of depressive pathology in the delusional and nondelusional groups. At admission the mean Hamilton score of the delusional depressive group was identical to that of the nonpsychotic depressive group (mean  $\pm$ SD=28.8 $\pm$ 9.6 versus 28.8 $\pm$ 9.7), and the discharge scores of the two depressive groups were also similar (7.0 $\pm$ 4.4 versus 7.5 $\pm$ 8.2). Similar results emerged for the BPRS. Although at hospital admission the delusional depressed patients were significantly more symptomatic according to the BPRS  $(mean \pm SD \ score = 28.3 \pm 11.0 \ versus \ 13.8 \pm 4.5; \ t =$ 3.73, df=21, p<.01), at hospital discharge the delusional depressed patients were only slightly more symptomatic (8.7 $\pm$ 6.0 versus 5.3 $\pm$ 3.2; t=1.54; df= 21, p<.20).

Significantly fewer of the nonpsychotic depressed patients were taking antipsychotic medications at follow-up ( $\chi^2=10.3$ , df=1, p<.001). Of the 31 delusional depressed patients, two (6%) were taking antidepressant medication alone, 12 (39%) were taking neuroleptics alone, and two (6%) were taking a combination of antidepressants and neuroleptics. Of the 28 nonpsychotic depressed patients, four (14%) were taking antidepressants alone, and two (7%) were taking a combination of antidepressants and reuroleptics. Of the 51 schizophrenic patients, three (6%) were taking antidepressants alone, 31 (61%) were taking neuroleptics alone, and three (6%) were taking a combination of antidepressants and neuroleptics. Of the delusional depressed patients, 54% were receiving psychotherapy at follow-up, as were 38% of the nonpsychotic depressed patients and 44% of the schizophrenic patients ( $\chi^2=0.31$ , df=2, p>.40).

In the current study the patients were not randomly assigned to treatment conditions but, rather, were often treated with medications or psychotherapy because of their clinical status. Thus, patients with more

severe psychopathology may have been more likely to receive treatment than were patients with fewer signs of severe illness at follow-up.

# Follow-Up Assessment

The follow-up evaluations, described elsewhere (2, 14), were performed blind with respect to diagnosis. To provide a uniform interval for the evaluations of posthospitalization adjustment, this assessment occurred at least 1 year after discharge for all patients and was conducted an average of 14 months after hospital discharge (range=12-26 months). The follow-up protocol consisted of a structured interview, a series of performance tests, several questionnaires, and a shortened version of the Schedule for Affective Disorders and Schizophrenia (SADS) (20). The follow-up test battery included detailed assessments of the following: 1) social functioning, instrumental work performance, and family adjustment, 2) psychotic and anxiety-neurotic symptoms and depressed mood, 3) posthospitalization psychotherapy and medication, and 4) rehospitalization.

Three global scales of overall outcome were used as the main measures of functioning. The first, developed by Levenstein et al. (21) and referred to as "the LKP scale," considers a number of primary areas of functioning after hospitalization, including work and social functioning, life disruptions, self-support, symptoms, relapse, rehospitalization, and suicide. The LKP scale takes into account the patient's level of functioning during the past year and thus is not limited to the patient's functioning during one select week or month. Scoring on the LKP outcome scale was performed by trained interviewers for whom adequate interrater reliability had been obtained (intraclass correlation coefficient=.92).

The second measure of overall outcome was derived from indices developed by Strauss and Carpenter (22). This measure provides a general overall picture of posthospital functioning based on adjustment in four specific areas: social adjustment, occupational functioning, rehospitalization, and symptoms. The measures of work performance and rehospitalization are based on the patient's functioning during the past year. The measures of social functioning and psychiatric symptoms are based on the patient's functioning during the past month. Indexes of global functioning in the week and month before the follow-up were also obtained from ratings by the interviewers on the Global Assessment Scale (GAS) (23) for 91 of the 110 patients.

The presence of mood-congruent and mood-incongruent delusions at the time of follow-up was determined from the SADS interview, which covers the 1 month before the interview. Delusions with content that was depressive, nihilistic, guilty and self-condemning, somatic, or referential (without persecution) were classified as mood-congruent. Delusions with content that was bizarre or persecutory or had themes

of thought withdrawal, thought insertion, or thought broadcasting were classified as mood-incongruent.

Information on anxiety-neurotic and depressive symptoms at follow-up was obtained from the Katz Adjustment Scale (24). This is a self-administered question-naire in which the patient uses a 4-point scale to rate the intensity of each of 55 symptoms during the previous 2 weeks. Of the 55 symptoms, 10 assess anxiety symptoms, and nine tap depressed mood and behavior. The scores used in the analysis were the sums of the patients' ratings on these two subscales.

Analyses of variance were computed to compare patient groups on major patient or outcome variables. A priori planned comparisons were used to compare the two depressive groups and to compare the delusional depressive group to the schizophrenic group.

#### RESULTS

#### Overall Outcome

Table 1 reports the results of the analyses of overall outcome. According to one-way analyses of variance (ANOVAs), there were significant main effects for diagnosis for both the LKP scale (F=7.00, df=2, 103, p<.002) and the Strauss-Carpenter scale (F=8.18, df=2, 103, p<.002). Separate analysis using the three different groups indicated that the schizophrenic group showed significantly worse functioning at follow-up on these scales of overall adjustment than both the delusional depressed patients (see table 1) and the nonpsychotic depressed group (LKP: F=10.53, df= 1, 103, p<.01; Strauss-Carpenter: F=11.89, df=1, 103, p<.001). Despite a slightly more pathological mean score for the delusional depressed patients than the nonpsychotic depressed subjects on each of the outcome scales, the two depressive groups did not differ significantly on overall outcome.

The results on the GAS were similar. The overall one-way ANOVA showed significant group differences (F=3.68, df=2, 88, p<.02). Individual a priori contrast tests again indicated that there was no difference between the delusional and nonpsychotic depressed patients, despite slightly poorer overall functioning by the delusional patients. The schizophrenic patients again had a significantly poorer outcome than the nonpsychotic depressed patients (F=5.26, df=1, 88, p<.02), but the difference between the schizophrenic and delusional depressed patients was not significant, although again there was a strong trend toward poorer functioning among the schizophrenic subjects (see table 1).

When considered in terms of overall outcome, these data suggest that there are only slight differences between the delusional and nonpsychotic depressed patients and that the delusional patients have slightly poorer overall functioning. Overall, the schizophrenic patients tended to show significantly poorer functioning at follow-up than the two depressive groups.

TABLE 1. Overall Outcome and Anxiety and Depressive Symptoms of 31 Delusional Depressed Patients, 28 Nonpsychotic Depressed Patients, and 51 Schizophrenic Patients 14 Months After Hospital Discharge

			Group	Score			Analysis of Variance					
		sional ession		ychotic ession	Schizop	hrenia		lusional Ve sychotic De			sional Dep sus Schizop	
Index	Mean	SD	Mean	SD	Mean	SD	F	df	р	F	df	p
Overall outcome												
LKP scale (21) <sup>a</sup>	4.3	2.50	4.0	2.72	5.8	1.94	0.29	1, 103	n.s.	7.29	1, 103	<.01
Strauss-Carpenter								,			•	
scale (22) <sup>b</sup>	10.9	3.52	11.5	3.64	8.5	3.58	0.56	1, 103	n.s.	7.99	1, 103	<.006
GAS (23) $(N=91)^b$	56.5	21.67	63.0	17.22	50.7	18.85	0.67	1,88	n.s.	2.78	1,88	.09
Katz Adjustment												
Scale (24)												
Depressed mood <sup>c</sup>	16.7	5.57	19.2	6.17	15.9	5.93	2.65	1, 102	<.10	0.27	1, 102	n.s.
Anxiety-neurotic												
symptoms <sup>c</sup>	15.1	4.81	17.9	5.25	16.7	4.91	4.33	1, 102	<.05	1.35	1, 102	n.s.

<sup>&</sup>lt;sup>a</sup>Higher score indicates poorer adjustment.

#### Affective and Anxiety Symptoms at Follow-Up

Results were obtained from the indexes of depressed mood and anxiety-neurotic symptoms from the Katz Adjustment Scale. As table 1 indicates, the delusionally depressed patients tended to have *less* severe symptoms of depressed mood than the nonpsychotic depressed group. The delusionally depressed patients did have more severe depressive mood than the schizophrenic patients, but the difference was not statistically significant. In contrast, the nonpsychotic depressed patient group had a significantly more depressed mood than the schizophrenic group (F=4.38, df=1, 102, p<.03).

The a priori planned comparison between the delusionally depressed and nonpsychotic depressed patients for anxiety symptoms revealed a statistically significant difference; the delusionally depressed patients had fewer or *less* severe symptoms. Surprisingly, the delusionally depressed subjects were somewhat *less* symptomatic on this index than were the schizophrenic patients, although this difference was not significant.

#### Presence of Delusions at Follow-Up

The presence of partial and full delusional ideation after hospitalization was determined from the SADS for both mood-congruent and mood-incongruent delusions (see table 2). When considering only mood-congruent, or depressive, delusions, there was a non-significant trend for more delusional activity at follow-up among the delusional depressed patients than among the nonpsychotic depressed patients. The difference between the groups would have been larger had it not been for two nonpsychotic depressed patients who showed partial or full delusional symptoms at follow-up.

Whereas the two depressive groups were similar in other areas, the delusionally depressed patients had a significantly higher prevalence of mood-incongruent delusions at follow-up. The results in this area of

TABLE 2. Mood-Congruent and Mood-Incongruent Delusions in 31 Delusional Depressed Patients and 28 Nonpsychotic Depressed Patients 14 Months After Hospital Discharge

Type of		sional d Patients	Nonpsychotic Depressed Patients		
Delusions	N	%	N	%	
Mood congruent <sup>a</sup>					
Absent	24	77	26	93	
Present	7	23	2	7	
Mood incongruentb					
Absent	19	61	24	86	
Present	12	39	4	14	

 $<sup>^{</sup>a}\chi^{2}=2.4$ , df=1, p=.12.  $^{b}\chi^{2}=3.8$ , df=1, p<.05.

outcome could be important, since many clinicians have questioned whether delusional depression is a more severe manifestation of an affective disorder or a different type of depressive disorder. If delusional depression at index hospitalization were only a sign of a tendency toward more severe depressions, then one might expect that these patients, who were more severely disturbed at the time of hospitalization, would subsequently manifest more severe affective symptoms and perhaps more severe anxiety symptoms as well at follow-up. This was not the case, which casts some doubt on the hypothesis that delusional depressed patients only have more severe depressions. Our data indicate that the delusional depressed patients did not have more severe affective symptoms and anxiety at follow-up. However, they did have a higher prevalence of delusions, particularly mood-incongruent delusions, suggesting a specific vulnerability to delusional and psychotic symptoms.

#### Rehospitalization

No statistically significant differences were noted in the frequency of rehospitalization among the groups.

<sup>&</sup>lt;sup>b</sup>Higher score indicates better adjustment.

<sup>&</sup>lt;sup>c</sup>Higher score indicates more severe psychopathology.

However, slightly more of the delusional than the nonpsychotic depressed patients had been rehospitalized, and both depressive groups had lower rates of rehospitalization than the schizophrenic patients.

These results indicate that delusionally depressed patients have an incidence and duration of rehospitalization that is not dramatically different from that of nonpsychotic depressed patients. Other investigators (6) have noted a higher number of previous hospitalizations for delusional depressed than for nonpsychotic depressed patients. The current results do not support a diagnostic distinction between these depressed groups on the basis of rehospitalization rate and are consistent with observations (7, 11) that these two groups may not differ in frequency of illness episodes. Further data are required to resolve this issue.

#### Social and Work Functioning at Follow-Up

The Strauss-Carpenter indexes of instrumental work functioning and social adjustment were used to investigate other areas of posthospitalization functioning. There were no statistically significant differences between the two depressive groups in instrumental work functioning. In contrast, the schizophrenic patients showed significantly poorer work functioning than either the delusional (F=12.0, df=1, 103, p<.001) or nonpsychotic (F=14.68, df=1, 103, p<.001) depressed patients.

As was true for instrumental work functioning, the two depressive groups were not distinguished by the degree of impairment of social adjustment at follow-up, although the delusionally depressed patients were somewhat less likely to have good outcomes in this area. The schizophrenic patients evidenced a poorer level of social functioning than the delusionally depressed group, although this difference was not statistically significant either.

#### **DISCUSSION**

The present research used follow-up data to begin providing clues bearing on two central questions. The first of these is whether there are differences in outcome between patients who are delusionally depressed at hospitalization and patients who are not psychotically depressed at hospitalization. The second question is whether being delusional at hospitalization is important in terms of later adjustment.

## Do Delusional Depressed Patients Differ From Nonpsychotic Depressed Patients?

The question of whether delusional depressed patients have a posthospital outcome that differs from that of nonpsychotic depressed patients received a somewhat mixed answer. In overall functioning for the entire posthospitalization period, the delusionally de-

pressed patients had scores that were between those of the nonpsychotic depressed patients and the schizophrenic patients. Except for the symptom picture at follow-up, however, the delusional depressive group was functioning at a level quite close to that of the nonpsychotic depressive group, and there were no significant differences between these two groups. The one area where the delusional depressed patients differed from the nonpsychotic patients was in the subsequent symptom picture. The delusional depressed patients showed fewer depressive and anxiety symptoms, and more of them had mood-incongruent delusions than did the nonpsychotic depressed patients. There were substantial group differences between the nonpsychotic depressed patients and the schizophrenic patients on all outcome measures.

Thus, the area of posthospitalization outcome that most clearly highlighted differences between the depressed groups was symptoms. Patients who were delusionally depressed in the acute phase were more likely than nonpsychotic depressed patients to have psychotic symptoms after hospitalization, particularly mood-incongruent symptoms. Some or many delusional depressed patients may be vulnerable to, or have a tendency toward, delusional thinking after hospitalization. It should be noted that 45% of the delusional depressed patients were receiving antipsychotic medication in significant amounts even 1 year after discharge. However, the majority of the delusional depressed patients did not show delusions or other psychotic symptoms at follow-up, despite their greater tendency in this direction.

The analyses of depressive and, particularly, anxiety-neurotic symptoms showed an unexpected tendency toward more psychopathology in the initially nonpsychotic patients.

These data further suggest that the course of psychotic and affective symptoms in delusional depression differs from that in nonpsychotic depression. It appears that for delusional depressed patients, affective and anxiety symptoms are *less* persistent and provide a smaller overall contribution to the total clinical picture 1 year after hospital discharge. For many nonpsychotic depressed patients, depressive symptoms appear to be somewhat more persistent and severe, possibly as a result of chronic depressive trends for some or many of them.

The results indicate that the psychotic symptoms seen in some patients with major depressive disorders may not be solely an epiphenomenon of a more severe affective disorder. Rather, these patients appear to have a disorder that involves a greater vulnerability to delusions and psychotic symptoms both at index hospitalization and at follow-up. There have been some reports (8, 11) of consistency in delusional ideation in recurrent illness and of ideational rumination about specific themes. It is possible that the delusional ideas of a subsample of these depressed patients persist and that others among these patients are vulnerable to subsequent delusional episodes.

Overall, these data on symptoms suggest that the two depressive groups do represent different types of disorders. It is possible that these somewhat surprising results may be influenced by chronic anxiety symptoms and chronic depressive trends in a certain number of the nonpsychotic depressed patients. This subgroup of nonpsychotic depressed subjects may have experienced anxiety symptoms and depressive trends for years before the more severe disorder seen at the time of index hospitalization, and these patients may have continued to experience some anxiety and depressive trends after hospitalization.

The results from other areas of posthospital adjustment (e.g., rehospitalization, social and work functioning) indicate that delusional depressed patients have aspects of functioning which resemble the functioning of nonpsychotic depressed patients. Thus, the delusional depressive group was highly similar to the nonpsychotic depressive group in the level of work performance, and each group was functioning significantly better than the schizophrenic patients. The social functioning of the delusional depressed subjects also was similar to that of the nonpsychotic depressed patients.

In most areas there were trends toward slightly poorer outcomes among the formerly delusional depressed patients than among the nonpsychotic patients. The differences were not significant, but there were significant differences in most major areas between either group of depressed subjects and the schizophrenic patients. Hence, the data did indicate similarities in specific areas of outcome for the initially delusional and nonpsychotic depressed patients and many areas in which they were indistinguishable. At the same time, there were a few areas involving their subsequent vulnerability to specific types of symptoms in which they were clearly distinguishable and possibly representative of somewhat different types of disorders.

### Does the Presence of Delusional Symptoms Predict Outcome?

The second major issue is whether delusional or other psychotic symptoms are important in general. Prominent theorists such as Pope and Lipinski (25) and Abrams and Taylor (26) have provided some evidence suggesting that psychotic symptoms are inconsequential or unimportant when considered in the context of the patient's subsequent functioning. Evidence on outcome by other research groups (1, 27) and by our own group (2, 14, 15) suggests that having psychotic, schizophrenic-like symptoms is of major consequence to the individual. The data on schizoaffective patients, who also have schizophrenic-like psychotic symptoms in addition to an affective disorder, have indicated that the presence of mood-incongruent psychotic symptoms also is important. Only a relatively small percentage of schizoaffective patients show a very good outcome in all areas of functioning (2).

The present data on major depressive disorders also suggest that the presence of delusional and psychotic symptoms affects posthospital functioning for this group of patients. This effect was observed in the different prevalences of delusions at follow-up in the patients with and without delusions during the index hospitalization. At least some initially delusional depressed patients appear to be more vulnerable to subsequent mood-incongruent delusions. It is possible that the consequence of having psychotic symptoms differs according to variables such as the quality, severity, or pervasiveness of such symptoms. Overall, however, when we look at the larger picture of delusions at hospitalization, our results suggest that while the presence of delusions is important in terms of specific vulnerability to psychotic symptoms, it is *less* important for subsequent overall functioning among depressed patients than it is for other groups with major pathology, such as schizophrenic and schizoaffective patients.

#### REFERENCES

- Coryell W, Lavori P, Endicott J, et al: Outcome in schizoaffective, psychotic and nonpsychotic depression: course over a sixto 24-month follow-up. Arch Gen Psychiatry 1984; 41:787–791
- Grossman LS, Harrow M, Lechert Fudala J, et al: The longitudinal course of schizoaffective disorders: a prospective follow-up study. J Nerv Ment Dis 1984; 172:140–149
- 3. Harrow M, Grossman LS: Outcome in schizoaffective disor ders: a critical review and reevaluation of the literature. Schizophr Bull 1984; 10:87–108
- Meltzer HY, Hyong WC, Carroll BJ, et al: Serum dopamine-βhydroxylase activity in the affective psychoses and schizophrenia. Arch Gen Psychiatry 1976; 33:585–591
- 5. Sweeney D, Nelson C, Bowers M, et al: Delusional versus nondelusional depression: neurochemical differences. Lancet 1978; 2:100-101
- Guze SB, Woodruff RA, Clayton PJ: The significance of psychotic affective disorders. Arch Gen Psychiatry 1975; 32:1147–1150
- 7. Frances A, Brown RP, Kocsis JH, et al: Psychotic depression: a separate entity? Am J Psychiatry 1981; 138:831-833
- Nelson JC, Bowers MB: Delusional unipolar depression: description and drug response. Arch Gen Psychiatry 1978; 35: 1321-1328
- 9. Glassman AH, Roose SP: Delusional depression: a distinct clinical entity? Arch Gen Psychiatry 1981; 38:424–42
- Weissman MM, Prusoff BA, Merikangas KR: Is delusional depression related to bipolar disorder? Am J Psychiatry 1984; 141:892–893
- Charney DS, Nelson JC: Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry 1981; 138:328–333
- 12. Glassman AH, Kantor SJ, Shostak M: Depression, delusions, and drug response. Am J Psychiatry 1975; 132:716-719
- 13. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
- 14. Kaskey GB, Nasr S, Meltzer HY: Drug treatment in delusional depression. Psychiatry Res 1980; 1:267–277
- Harrow M, Grinker RR Sr, Silverstein ML, et al: Is modern-day schizophrenic outcome still negative? Am J Psychiatry 1978; 135:1156-1162
- Grinker RR Sr, Harrow M (eds): Clinical Research in Schizophrenia: A Multidimensional Approach. Springfield, Jll. Charles

C Thomas (in press)

 Harrow M, Quinlan D: Disordered Thinking and Schizophrenic Psychopathology. New York, Gardner Press, 1985

- Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773–782
- Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799-812
- Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
- Levenstein S, Klein DF, Pollack M: Follow-up study of formerly hospitalized voluntary psychiatric patients: the first two years. Am J Psychiatry 1966; 122:1102–1109
- 22. Strauss JS, Carpenter WT: The prediction of outcome in

- schizophrenia. Arch Gen Psychiatry 1972; 27:739-746
- Endicott J, Spitzer RL, Fleiss JL: The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33:766–771
- 24. Katz M, Lyerly S: Methods for measuring adjustment and social behavior in the community, I: rationale, description, discriminative validity, and scale development. Psychol Rep 1963; 13: 503-535
- Pope HG, Lipinski JF: Diagnosis in schizophrenia and manicdepressive illness. Arch Gen Psychiatry 1978; 35:811-828
- Abrams R, Taylor MA: Importance of schizophrenic symptoms in the diagnosis of mania. Am J Psychiatry 1981; 138:658–661
- Coryell W, Tsuang MT, McDaniel J: Psychotic features in major depression: is mood congruence important? J Affective Disord 1982; 4:227–236

### Behavioral Aspects of Panic Disorder

Isaac M. Marks, M.D.

The behavioral approach to panic disorder distinguishes between agoraphobia and nonsituational panic and emphasizes the handicap to the patient caused by avoidance of agoraphobic situations. Agoraphobia is a more viable label than panic disorder. Behavioral treatment consists of delineating the patient's agoraphobic avoidance and panic profile and developing a self-exposure program to produce habituation. Systematic exposure to agoraphobic situations is usually of durable efficacy, and the treatment requires little time from clinicians. Antidepressant drugs, which do not interfere with exposure, are a useful addition when dysphoria is present, but they can have troublesome side effects. (Am J Psychiatry 1987; 144:1160–1165)

The DSM-III notion of panic disorder has stimulated immense interest in a common yet puzzling group of problems which share much with both phobic

disorders and generalized anxiety. For the category panic disorder, it is assumed that panic is a cardinal feature in an entity with a specific etiology, phenomenology, and treatment. In protean problems such as these, it is hard to guess which element to seize as the Ariadne's thread that will guide us out of the labyrinth.

Panic in the anxiety disorders seems like anemia or arthritis in blood or joint disorders. Observers can reliably agree on the presence of panic, anemia, or arthritis, but reliability need not imply validity. The presence of panic predicts little about phenomenology, etiology, or treatment, and its discontinuity from anxiety may have been exaggerated.

The behavioral approach offers another way of looking at these problems that makes better sense of the phenomenology and gives a clear guide to simple and enduringly effective treatment. It distinguishes phobic and nonphobic panic from the characteristic agoraphobic avoidance that is a central handicap in most cases and tells us how to help these patients.

#### **PHENOMENOLOGY**

Two types of panic are seen in panic disorder: phobia (situational) and nonsituational. The former, which occurs in the great majority of cases (i.e., those patients who have panic disorder with agoraphobia), is predictably triggered by a characteristic cluster of agoraphobic situations that mainly involve public

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places ("agora" is the Greek word for marketplace), such as the street, stores, public transport, theaters, and crowded or enclosed spaces. Agoraphobic patients may not panic in all such situations but always do in some of them; multiple fears from within that cluster of cues are pathognomonic.

The situations that evoke phobic panic in agoraphobic patients may be either real or imagined; i.e., phobic panic can be induced either by 1) actually going into those situations or by 2) merely thinking about entering them. The latter is "anticipatory phobic panic" similar to the panic that will strike someone with a severe cat phobia on thinking about cats or a normal mother on thinking that her child has had an accident.

A critical concomitant of phobic panic in all phobias, including agoraphobia, is avoidance of those cues that regularly trigger panic. This leads to handicap if the avoided situations are frequent in everyday life, which is the case in agoraphobia. It is easier for an individual with a cat phobia to carry on normal life while avoiding cats than it is for an agoraphobic person, who avoids public places. This avoidance leads many agoraphobic people to become completely housebound.

Situational (phobic) panic, including anticipatory panic, is a hallmark of almost all severe phobias, not merely of the agoraphobia that is present in most cases of panic disorder. The subjective, behavioral, and physiological features of phobic panic are similar across the various types of phobia (1); indeed, the same features appear in normal panic as in soldiers under bombardment. Almost all phobic persons experience rapid heart rate and breathing, sweating, and an urge to run away, and they may be frozen in terror for part of the time. The panic of agoraphobia is wellknown. Less well known but equally dramatic is the panic experienced by those with specific phobias when confronted with their phobic stimulus. For example, when a spider suddenly landed on them, spider phobic patients of mine have jumped off a galloping horse in a forest, leapt out of a boat into the sea even when unable to swim, or scrambled on top of the kitchen refrigerator and remained petrified there for hours until help came.

Another insufficiently appreciated point is that in agoraphobia, as in all phobias, relevant phobic cues evoke discomfort that ranges from mild anxiety to severe panic. Differing degrees of situational anxiety and situational panic are not clearly delineated; they fall on a continuum of severity, shading into one another. (Henceforth, the term "panic" will include lesser degrees of anxiety too.) By definition, situational panic is not found in nonphobic individuals. No one has yet shown that the distinction between mild anxiety and severe panic is more categorical than the distinction between mild pain and excruciating agony. Mild and severe trigeminal neuralgia are not separate conditions.

Given that the panic ensuing from contact with the phobic situation is so similar across the various types of phobia, is there anything distinctive about the situational panic of agoraphobia/panic disorder? The answer is the particular constellation of situations that bring it on. Agoraphobic persons are not frightened by encountering real or imagined cats, thunderstorms, or dirt, but they are terrified when in the street, theater, or subway, or among crowds. In contrast, those with a cat phobia are not frightened of public places—only cats—while those with a thunderstorm phobia fear not public places but thunderstorms.

Nonsituational panic, the second type, is found in all cases of panic disorder, whether or not these patients have agoraphobia. This panic occurs with no clear trigger; variants have been called nonsituational, non-phobic, unexpected, unpredictable, uncued, spontaneous, or free-floating panic. Insofar as everything has a cause, there must be some hidden trigger for such panic, but that trigger is not a particular external situation or thought about such a situation. Speculations about possible precipitants of nonsituational anxiety range from discharges in the locus ceruleus to unconscious fantasies. Such speculations are hard to evaluate in the absence of good controlled data.

A continuum between nonsituational anxiety and nonsituational panic corresponds to that in situational (phobic) anxiety, with respect to both duration and intensity of the discomfort. Tonic tension and surges of nonsituational panic merge into one another and are highly correlated.

Nonsituational panic may occur without agoraphobia (yielding the DSM-III-R category of panic disorder without agoraphobia) and is also common in major depression. Most agoraphobic persons have had non-situational as well as situational anxiety, often of sufficient severity to be called panic.

#### Relation of Agoraphobia to Other Phobias

Agoraphobia shares with other phobias the presence of phobic panic and avoidance. However, as mentioned, the cues evoking such panic and avoidance tend to be different. First, the cues are a characteristic cluster of public places. Second, the cues are more multiple. Third, unlike most other phobic individuals, those with agoraphobia tend to have more nonphobic anxiety-related symptoms, including nonsituational panic, tonic tension, depression, and depersonalization.

#### Relation of Agoraphobia to Panic Disorder

DSM-III-R agoraphobia is both a subset of panic disorder (panic disorder with agoraphobia) and an entity outside of it (agoraphobia without a history of panic disorder). Little commends this spurious division. There is no evidence that agoraphobia without a history of panic disorder (in which the nonsituational and situational have never reached panic levels) differs substantively from agoraphobia in which such anxieties have reached the intensity of panic. After all, mild

and severe rheumatoid arthritis are not separate disorders.

There is good reason, however, to separate agoraphobia from panic disorder without agoraphobia, despite the many intermediate cases. Unlike pure panic disorder patients, agoraphobic persons not only panic in certain situations but also tend to avoid them, and it is this avoidance which gives rise to their disability: their gradual confinement to the home because places outside bring on panic. They may even panic at home, but this is much less likely. Rarely, those with agoraphobia actually avoid sleeping in their beds once they have had a panic there, but examples like this are great exceptions. Avoidance is far more likely to develop to outside than to home situations in which panic has been experienced. As a species we may be more prepared to link panic to places outside our home territory than inside it, though this is probably not the whole story. It is hard to discern a common theme in the agoraphobic cluster. Saying that agoraphobic people seek safety begs the question of why home seems so much safer than places outside it, even when panic occurs at home.

We do not know why the nonsituational panic of panic disorder often gets conditioned to the situations in which it occurs, transforming into the situational (phobic) panic and avoidance so typical of agoraphobia, while a minority of cases remain pure panic disorder without developing agoraphobia. A prospective follow-up of cases right from the start might clarify that conundrum.

Many cases of agoraphobia do share the nonphobic symptoms of panic disorder—nonsituational panic, tonic tension, depression, and depersonalization—and this overlap may partly account for the *DSM-III-R* mode of labeling.

The various types of onset of agoraphobia resemble those found in other phobic disorders and in obsessivecompulsive disorder. Although many believe that agoraphobia always starts with a series of unexpected panics, in many cases early episodes may merely consist of twinges of mild anxiety that gradually mounts in intensity over successive episodes until one day it becomes a complete panic. Other cases begin with complete panic, and from that moment the person avoids the place where it occurred, so that only the first panic is unexpected. Thereafter, escape reduces panic and so reinforces further escape and ultimately avoidance. What initiates the original discomfort is still obscure. Dysphoria for whatever reason can potentiate it, but some agoraphobic patients deny ever having been depressed.

Agoraphobia with a stuttering onset reminds us of kindling in animals; intermittent electrical stimulation of the amygdala eventually elicits a seizure, after which even previously subthreshold levels of stimulation trigger a fit. It may take a massive panic in an actual store to precipitate avoidance of that store the first time there, but after several trials even just thinking of that situation will precipitate panic.

#### Reasons to Retain Agoraphobia as a Prime Diagnostic Label

There are strong reasons to retain the diagnostic category of agoraphobia that Westphal coined well over a century ago. Although the syndrome is protean—the exact cluster of phobias varying from one patient to the next—the agreement about its "fuzzy" set of features has been impressive in many multivariate analyses in the United States and Europe (2–7, and Lipman et al. 1979 work cited by Hallam [4]). Simply knowing that someone fears going into the street and stores predicts his or her liability to show many other phobic and nonphobic aspects of that syndrome.

A similar research base does not underpin the DSM-III-R label of panic disorder, and the term might best be abandoned inasmuch as it covers such a wide range of conditions. Nearly all phobic persons have at some point had unexpected panic on encountering their phobic stimulus, while nonsituational panic is frequent in major depression and during withdrawal from alcohol or opiates and also occurs during hyperventilation and in vestibular disorders. Only a handful of panic disorder patients have no agoraphobia. They may have more somatic anxiety complaints and more muscular tension than do persons with generalized anxiety disorder (8), but this hardly seems reason enough to give them a separate diagnostic label (just as the presence or absence of nodules in rheumatoid arthritis is no reason to divide it into two diagnostic entities). It is not very informative to say that someone has panic. Is it phobic panic, and if so, what type? Is it nonsituational panic? Is it part of depression or alcohol withdrawal or even of obsessive-compulsive disorder?

Close scrutiny indicates that panic disorder has no distinct etiology, genetic background, biological marker, or treatment that clearly separates it from other anxiety disorders (reviewed by Marks [9]). The familial loading in panic disorder is not of panic disorder per se but of a variety of anxiety disorders and depression. Disagreement is great about the frequency of mitral valve prolapse in panic disorder compared to that in other populations. No biological marker has been shown to be present solely in panic disorder and not in agitated depressed or anxious obsessive-compulsive patients or normal people panicking during real danger. This caveat concerns both panic response to sodium lactate infusion and left-right asymmetric blood flow in the parahippocampal gyri during panic. Panic response to lactate infusion occurs in anxious depression as well as in panic disorder and has been abolished not only with drugs but also with exposure therapy. There is no drug that exclusively helps panic disorder and no other syndrome.

Phobic and nonphobic features vary among the phobic disorders, including agoraphobia, panic disorder without agoraphobia, and obsessive-compulsive disorder. Panic (phobic and/or nonsituational) is found in all these conditions, while phobic panic and avoid-

ance are absent in pure panic disorder but present in phobic and obsessive-compulsive disorder. Nonphobic anxiety and depression are especially common in agoraphobia, panic disorder without agoraphobia, and obsessive-compulsive disorder.

#### TREATMENT

A great strength of the behavioral approach to panic disorder is its rapid effectiveness in treating most cases. Controlled trials in the United States and Europe have repeatedly found that agoraphobic patients do well after exposure treatment for up to 4–7 years of follow-up, which is far longer than any results reported after discontinuation of drug treatment. The relative success of live exposure therapy does not, of course, tell us much about the cause of agoraphobia, though it may hint that avoidance maintains disability once the problem has begun.

The value of exposure is still less well known and used by psychiatrists than it might be. One reason may be our adherence to a medical model that searches for a curative drug. Unless we integrate the biological perspective with a psychosocial one, however, we are likely to err and may fail to give our agoraphobic patients a fair deal.

Other reasons for resistance to adopting exposure therapy might be beliefs that it requires a detailed knowledge of learning theory that few psychiatrists possess and that it is too time-consuming for busy clinicians. Neither of these notions is borne out by experience. In the last few years, hundreds of clinicians in the United Kingdom have learned to give exposure therapy successfully without having been trained in learning theory and after very brief instruction in exposure methods. Moreover, these effective applications often required the clinician to devote no more time to the patient than is customary with drugs and other widely used forms of psychiatric treatment. Within days of instruction many clinicians become able to find ways of helping agoraphobic patients in routine clinics by fairly simple advice about the exposure principle.

#### The Self-Help Model

This encouraging development partly arose from a recent move away from the idea of behavioral treatment as something done to patients toward a realization that behavioral methods form a system of self-help that the patient learns from a clinician who largely acts as coach and monitor. In most cases of agoraphobia, there is no need to practice exposure with the patients in the phobic situation, only to guide them on what to do there. The majority of patients can carry out the practice part of the treatment without a clinician being present.

The clinician starts by mapping the patient's agoraphobic avoidance profile ("What do you avoid because

it causes anxiety or panic in you but not in most other people?"). This is the first step in developing an exposure treatment strategy to yield lasting relief from disability without needing much time from the clinician. Next, the clinician explains to the patient (and a relative, too, if one is available as a cotherapist) how he or she can overcome the problem by a self-exposure program that will deal with each part of the avoidance profile in detail. Avoidance of and escape from frightening situations perpetuate panic, preventing patients from learning that if they allowed themselves to stay there long enough, the panic would subside anyway.

The patient's task is to remain in panic-inducing situations until he or she feels a bit better. This exposure will be more effective if it continues for long rather than short periods. The exercise should be repeated regularly until the fear is at an acceptable level. Because the task is difficult, the patient can start self-exposure with less frightening situations, extending the program as he or she gets used to them. The program is most effective when the patient is not taking alcohol or benzodiazepines. It can be helpful for the clinician to prescribe the first few exposure tasks, which the patient freely agrees could be completed; the patient then sets more tasks as the earlier ones are completed.

The therapist asks the patient to use a suitable manual as a guide in the self-exposure program and to record every day in a structured but simple diary the exposure tasks carried out and their outcome. Patients then leave the clinic to practice the suggested exposure tasks as homework between sessions while keeping a daily record of this homework and its results. They bring this exposure-homework diary back to the therapist in the next session for discussion and suggestions on how to proceed further. Sometimes it is also helpful for patients to phone the therapist once or twice between sessions to make an interim report on progress and setbacks and to get ideas on how to deal with these. The patient is taught to anticipate setbacks and how to manage them.

Even severe agoraphobia can respond with very little therapist investment, merely appropriate advice, as demonstrated by the following example.

Case 1. Ms. A, a 40-year-old woman, had been virtually housebound for 5 years because of classic agoraphobia. In a 11/2-hour session, she, her husband, and I delineated her avoidance profile (those places she avoided regularly because they evoked panic) and worked out an exposure-homework program in which she would slowly habituate to one situation after another. I explained how she should keep a diary of her exposure-homework exercises and asked her to mail them to me. This she did regularly. She diligently carried out her exposure program and within weeks was mobile for the first time in years. She kept up her progress for 4 years without seeing me again, but then she had some family difficulties, which depressed her, and quickly relapsed. She saw me once more for an hour and was encouraged to revive her original exposure-homework program. On doing this she recovered her gains, which continued through follow-up for

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9 years, when I last heard from her—a gratifying result for 21/2 hours of time from a clinician.

Such results have been obtained by many clinicians who have used exposure therapy. These are far from being stories of miracle cures. Though little time is needed from the clinician, the patient has to work hard to implement the exposure program; improvement is only hard won by systematic self-implementation over many days and weeks and perhaps months. Ms. A's story illustrates what might be achieved by means of minimal intervention of the right kind for the right type of problem. This cannot be stressed too much. We are not talking about a vague placebo effect in which saying almost anything soothing might do the trick. Antiexposure instructions, for example, do not help phobic patients, nor does advice to relax. When such patients were advised to take a break from panic and to avoid whatever was upsetting them, they did not improve, although these same people did improve after they had embarked on an exposure program (10).

Patients who respond to brief exposure guidance as just illustrated are not rare. A general psychiatrist who is alert to the possibilities of behavioral psychotherapy will frequently find agoraphobic patients who can benefit from detailed exposure advice that is individually tailored to their particular problem.

The amount of behavioral help that agoraphobic patients need from a clinician varies enormously. Many sufferers merely lack the knowledge of what principle to apply; when they learn what to do from a clinician or read a suitable self-exposure manual, they can apply their new knowledge successfully without further help, devising and completing a methodical self-exposure program entirely on their own. Detailed manuals and diaries to record exposure homework help sufferers to execute their program properly. In planning a self-exposure program, phobic individuals have to remember that long exposure periods reduce panic more than shorter ones do.

Some agoraphobic patients need a bit of prompting to start a self-exposure program and then can manage on their own. Others require a little more help from the clinician in monitoring their progress at intervals. Clinicians need to teach patients to expect setbacks and rehearse dealing with them alone, but be available for the occasional brief booster session that some people require. All of these patients can be treated reasonably easily by a general psychiatrist without the need to refer them to a behavioral specialist and without medication.

When these patients do need additional help in the form of some therapist-aided exposure, most general psychiatrists might want to call in specialist help. A few such patients want to continue therapist-aided exposure indefinitely despite having repeatedly habituated during sessions; the long-term outcome in such cases is dubious, as eventually the therapist must fade out of the scene.

At least 15 controlled studies have found self-expo-

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sure therapy to be helpful for agoraphobia, and only one found no benefit from it (reviewed by Marks [9]). In the largest controlled study (11), marked gains from self-exposure occurred despite the patients' having no interaction with a clinician beyond initial screening. Forty chronic agoraphobic subjects were randomized to get self-exposure instructions over 10 weeks from a self-help book (Living With Fear [12]), a psychiatrist, or a computer. Apart from a 11/2-hour initial assessment, mean clinician time per patient in the three groups was, respectively, only 0, 1.6, and 1.5 hours. All three groups improved markedly and equally up to 6 months follow-up (11). Neither the clinician nor the computer conferred any advantage over the manual. Gains from self-exposure without medication were of the same order as those obtained using therapist-aided exposure or antidepressive drugs.

An obvious question is whether the three treatment conditions in the Ghosh and Marks study (11) were anything more than a placebo. The answer is that in other controlled studies, phobic subjects who expected to improve with another procedure (antiexposure) failed to get better (10), and indeed antiexposure almost abolished gains from imipramine in agoraphobic patients (13). Improvement from self-exposure is thus due less to the mere expectation of improvement than to the component of exposure that causes panic

to subside.

Self-exposure seems to yield enhanced results if patients use an appropriate manual and diary that records homework tasks for regular review. Still to be tested is the value of reading a manual without any prompting from a clinician. Two patients in the bookinstructed condition of Ghosh et al. (14) had in fact previously bought the book Living With Fear on their own initiative but had failed to follow its directions until they were asked to do so by the psychiatrist in the trial, so initial contact with a clinician is an important motivator for some people.

The efficacy of systematic self-exposure for agoraphobia is not yet widely realized. Obviously, failures do occur, but these are exceptional. Residual problems are not usually marked, and there is no controlled evidence that adding therapist aid to self-exposure enhances long-term outcome for most patients. The need to give therapist-aided exposure for agoraphobic patients has diminished as self-exposure manuals have been refined. Patients on my waiting list are asked to first try treating themselves using Living With Fear as a manual, and not infrequently they improve enough to obviate the need for a therapist. For most of the remaining cases, the clinician's role is to assess the problem and to teach people how to help themselves

Some clinicians add cognitive strategies to exposure therapy, identifying patients' abnormal beliefs and trying to modify them. In most controlled studies this practice failed to improve outcome of phobias or panic; moreover, abnormal beliefs were reduced as rapidly when panic was treated with exposure alone as

they were when cognitive therapy was added to exposure (9). Relaxation, too, is redundant. Perhaps a more promising current trend is brief training of patients to breathe slowly and regularly when anxious (15). Unpublished controlled work suggests this may be useful, but the point needs further controlled study.

Can behavioral treatment offer anything to the minority of panic disorder patients who have no agoraphobia? In theory, habituation might occur with a program of exposure to fantasies of internal cues of panic. Such an approach remains to be tested in systematic controlled trials with adequate follow-up. Research on this point is long overdue.

#### Drugs With Behavioral Treatment

There is little doubt that antidepressants help agoraphobic patients who are dysphoric, at least in the short term (16) (whether benzodiazepines are more than palliative remains to be seen). There is disagreement about whether antidepressants help agoraphobic patients who have normal mood (17, 18). Antidepressants do best when given together with exposure instructions (13, 19).

Most investigators report a high relapse rate once drug treatment is stopped, whereas relapse is not a major problem after exposure. This is crucial in weighing the trade-offs of various treatments in a condition as chronic as agoraphobia. The mean duration of agoraphobic symptoms in most controlled studies was nearly a decade or longer; in such cases the brief gains reported by most drug studies are of limited interest. The enduring gains after exposure are a more convincing benefit. Moreover, exposure has none of the drug side effects that make many agoraphobic patients refuse medication, nor does it carry the opposite risk of drug dependence that is present with benzodiazepines.

In brief, the handicap in panic disorder with agoraphobia stems mainly from avoidance of public places and is reliably treated by systematic exposure; antidepressants are helpful adjuvants when mood is disturbed.

#### REFERENCES

- 1. Öst L-G, Hugdahl K: Acquisition of blood and dental phobia and anxiety response patterns in clinical patients. Behav Res Ther 1985; 23:27-34
- 2. Marks IM, Mathews AM: Brief standard self-rating for phobic patients. Behav Res Ther 1979; 17:263-267
- 3. Hallam RS, Hafner RJ: Fears of phobic patients: factor analyses of self-report data. Behav Res Ther 1978; 16:1-6
- 4. Hallam RS: Anxiety: Psychological Perspectives on Panic and
- Agoraphobia. New York, Academic Press, 1985
  5. Dixon JJ, De Monchaux C, Sandler J: Patterns of anxiety. Br J Med Psychol 1957; 30:34–40, 107–112
- 6. Schapira K, Kerr TA, Roth M: Phobias and affective illness. Br J Psychiatry 1970; 117:25-32
- 7. Derogatis LR, Cleary PA: Factorial invariance across gender in the SCL-90. Br J Soc Clin Psychol 1977; 16:347-356
- Barlow DH, Cohen AS, Waddell MT, et al: Panic and generalized anxiety disorders: nature and treatment. Behavior Therapy 1984; 15:431-449
- 9. Marks IM: Fears, Phobias and Rituals. New York, Oxford University Press, 1987
- 10. Greist J, Marks IM, Berlin F, et al: Avoidance versus confrontation of fear. Behavior Therapy 1980; 11:1-14
- Ghosh A, Marks IM: Self-directed exposure for agoraphobia: a controlled trial. Behavior Therapy 1987; 18:3-16
- 12. Marks IM: Living With Fear. New York, McGraw-Hill, 1978
- 13. Telch M, Agras WS, Taylor CB, et al: Combined pharmacological and behavioral treatment for agoraphobia. Behav Res Ther 1985; 23:325-335
- 14. Ghosh A, Marks IM, Carr AC: Self exposure for phobias. Br J Psychiatry (in press)
- 15. Rapee RM: A case of panic disorder treated with breathing retraining. J Behav Ther Exp Psychiatry 1985; 16:63-65
- 16. Marks IM: Are there anticompulsive or antiphobic drugs?
- review of the evidence. Br J Psychiatry 1983; 143:338-347
  17. Marks IM, Gray S, Cohen D, et al: Imipramine and brief therapist-aided exposure in agoraphobics having self-exposure homework. Arch Gen Psychiatry 1983; 40:153-162
- 18. Solyom L, Solyom C, LaPierre Y, et al: Phenelzine and exposure in the treatment of phobias. Biol Psychiatry 1981; 16:239-247
- 19. Mavissakalian M, Michelson L: Agoraphobia: therapist-assisted in vivo exposure and imipramine. J Clin Psychiatry 1986; 47:117-122

## Clinical Comparison of Tourette's Disorder and Obsessive-Compulsive Disorder

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The authors report on 16 outpatients with Tourette's disorder, 16 outpatients with obsessive-compulsive disorder, and 16 normal control subjects who underwent structured interviews and psychological testing. Previous findings of a high incidence of obsessive-compulsive disorder in patients with Tourette's disorder were confirmed. There was a significantly greater incidence of tics in the patients with obsessive-compulsive disorder and their relatives. Both patient groups had high rates of unipolar depressive and generalized anxiety disorders. Panic and phobic disorders were frequent in the patients with obsessive-compulsive disorder but not in the patients with Tourette's disorder. The patients with obsessive-compulsive disorder showed less coprolalia, echo phenomena, self-destructive behavior, and childhood attention deficit.

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The relationship between tics and obsessions and compulsions has been of interest at least since the turn of the century (1). Recent studies (2) have found rates of obsessive-compulsive disorder in patients with Tourette's disorder (the most prominent tic disorder) ranging from 55% to 74%. The occurrence of tics in obsessive-compulsive disorder has occasionally been noted (3–5). Rasmussen and Tsuang (6) reported a 5% incidence of Tourette's disorder in patients with obsessive-compulsive disorder. The occurrence of other tic disorders and of associated features of Tourette's

disorder, such as coprolalia, echo phenomena (echolalia, echopraxia, palilalia), attention deficit, and selfdestructive behavior (7), in obsessive-compulsive disorder does not appear to have been examined.

DSM-III recognizes that Tourette's disorder may be accompanied by obsessive doubting thoughts and compulsive impulses to touch things or to perform complicated movements. DSM-III uses the criterion of purpose to distinguish compulsions from tics, defining compulsions as "designed to produce or prevent some future event or situation" (p. 235) and tics as "purposeless" and "involuntary" (p. 77). In a departure from its atheoretical stance with regard to the etiology of mental disorders, DSM-III excludes the diagnosis of obsessive-compulsive disorder if it is due to Tourette's disorder.

Despite a good deal of published commentary regarding the relationship between the two disorders, we are aware of no previous studies systematically comparing patients with obsessive-compulsive disorder and patients with Tourette's disorder.

#### **METHOD**

Subjects with Tourette's disorder were recruited from the Behavioral Neurology Clinic of the Beth Israel Hospital in Boston, and subjects with obsessive-compulsive disorder were recruited from the Obsessive-Compulsive Disorders Clinic of the Massachusetts General Hospital in Boston. Letters were sent to current and former adult patients of both clinics soliciting their participation. Patients were told that the study would involve a psychiatric interview and psychological testing but not that the relationship among Tourette's disorder, tics, and obsessions and compulsions would be explored. From the patients who responded to the letter, subjects were selected on the basis of scheduling convenience and an attempt to include equal numbers of men and women.

Of 49 patients with Tourette's disorder contacted, 20 expressed interest and 16 were interviewed. Fifteen of these met *DSM-III* criteria for Tourette's disorder. The sixteenth deviated only in that she denied having the ability to suppress her movements voluntarily. Because her signs and symptoms were typical of

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Tourette's disorder in all other respects, she was retained in the Tourette's disorder group. Of 32 patients with obsessive-compulsive disorder contacted. 22 expressed interest and 16 were interviewed. Fifteen met DSM-III criteria for obsessive-compulsive disorder. The sixteenth met criteria for not only obsessivecompulsive disorder but also Tourette's disorder. Because this subject was ascertained as an obsessivecompulsive patient, he was retained in the obsessivecompulsive group. Sixteen control subjects were recruited from the staff of a Veterans Administration (VA) Medical Center. None met DSM-III criteria for obsessive-compulsive disorder, Tourette's disorder, or any other psychiatric illness (excluding adjustment disorders), except for one who had a history of major depressive disorder.

There were eight male and eight female subjects in the obsessive-compulsive disorder and control groups. The Tourette's disorder group contained nine men and seven women. The mean ±SD age for the patients with Tourette's disorder was 31.0±7.8 years; for the patients with obsessive-compulsive disorder it was  $40.0\pm12.1$  years; and for the control subjects it was  $39.0\pm9.2$  years. The difference in age between patients with Tourette's disorder and patients with obsessivecompulsive disorder was significant (t=2.4, df=30, p=.02); so was the difference in age between patients with Tourette's disorder and the control subjects (t=2.7, df=30, p=.01). There were no significant differences between the groups in level of education. The mean±SD number of years of education for the patients with Tourette's disorder was 14.0±2.9 years; for the patients with obsessive-compulsive disorder it was  $13.6\pm2.3$  years; and for the control subjects it was  $14.8 \pm 2.7$  years.

After one of us (R.K.P.) explained the nature of the procedure and obtained informed consent, he interviewed each subject using the Yale Schedule for Tourette and Other Behavioral Syndromes-R (adult version) (unpublished 1985 manuscript of Pauls and Hurst, available on request through R.K.P.). This 113-page instrument contains detailed questions regarding lifetime history of tics, obsessions, compulsions, echolalia, echopraxis, palilalia, coprolalia, and childhood attention deficit and hyperactivity. It also includes the Diagnostic Interview Schedule (8), which incorporates DSM-III criteria for mental disorders. Subjects were also interviewed by using a supplementary interview schedule (unpublished 1985 form developed by R.K.P., available on request) concerning subjective experiences of Tourette's disorder and obsessive-compulsive disorder, pathological doubt, slowness, depersonalization, and self-destructive behaviors. Subjects also completed the following selfadministered psychometric instruments: the Maudsley Obsessive Compulsive Inventory (9), the Eysenck Personality Inventory (10), and the trait portion of the State-Trait Anxiety Inventory (11).

Following the interview regarding the subjects' own history, the descriptions of tics, obsessions, and com-

pulsions from the Yale schedule were reviewed with the subjects and they were asked whether to their knowledge any of their first-degree relatives (parents or siblings) had ever suffered from any of these symptoms. When the answer was positive, details were requested and the corresponding diagnostic criteria were applied. Family history was confirmed by telephone interview with a family member designated by the patient as a good historian whenever one was available, which was in 75% of the families (evenly distributed across the three groups).

All disorders and symptoms reported here for subjects and relatives are in terms of lifetime incidence. Except where indicated otherwise, results were analyzed for significance by means of one-tailed Fisher's exact tests.

#### **RESULTS**

Obsessive-Compulsive Disorder in Patients With Tourette's Disorder

Table 1 presents the numbers of subjects in the Tourette's disorder, obsessive-compulsive disorder, and control groups who met criteria for obsessivecompulsive disorder, Tourette's disorder, and any tic disorder, as well as the numbers of subjects with associated symptoms and other mental disorders. Four men and six women with Tourette's disorder met criteria for obsessive-compulsive disorder (we disregarded the criterion of exclusion of the obsessivecompulsive disorder diagnosis in the presence of Tourette's disorder). Four of the five patients with Tourette's disorder with coprolalia met criteria for obsessive-compulsive disorder. For the patients with Tourette's disorder who also had obsessive-compulsive disorder, the mean±SD age at onset of tics was 8.3±3.3 years and the mean±SD age at onset of obsessions/compulsions was 17.4±6.6 years. The symptoms of obsessive-compulsive disorder in these patients with Tourette's disorder were mixed and characteristic of patients with obsessive-compulsive disorder in general (6, 12). Their obsessions involved forbidden sexual and aggressive images and impulses; their compulsions included checking, washing, and counting as well as magical attempts to ward off feared events.

Table 2 presents the number of probands' parents and siblings with a history of obsessive-compulsive disorder or any tic disorder.

Tic Disorders in Patients With Obsessive-Compulsive Disorder

Five men and one woman with obsessive-compulsive disorder met criteria for any tic disorder (three chronic motor, two transient, one Tourette's disorder) (for the male-female difference, p=.06). Only one control subject (a man) met criteria for tic disorder (chronic

TABLE 1. Lifetime Occurrence of Psychiatric Disorders and Symptoms in 16 Patients With Tourette's Disorder, 16 Patients With Obsessive-Compulsive Disorder, and 16 Normal Control Subjects

	Subjects W	ith Lifetime Oc	ccurrence	Difference Between Groups (p) <sup>a</sup>			
Disorder or Symptom	Tourette's Disorder	Obsessive- Compulsive Disorder	Control	Tourette's vs. Obsessive- Compulsive	Tourette's vs. Control	Obsessive- Compulsive vs. Control	
Disorders of main interest							
Obsessive-compulsive disorder	10	16	0	n.s.	<.001	<.001	
Tourette's disorder	16	1	0	<.001	<.001	n.s.	
Any tic disorder	16	6	1	<.001	<.001	<.05	
Associated symptoms							
Pathological doubt	11	14	1	n.s.	<.001	<.001	
Slowness	10	13	1	n.s.	<.01	<.001	
Depersonalization	10	6	1	n.s.	<.01	<.05	
Compulsive touching	14	4	0	<.001	<.001	n.s.	
Self-destructive behavior	8	2	0	<.05	<.01	n.s.	
Coprolalia	5	0	0	<.05	<.05	n.s.	
Echo phenomena	10	2	0	<.01	<.001	n.s.	
Childhood attention deficit	7	2	0	n.s.	<.05	n.s.	
Symmetry behavior	10	4	0	<.05	<.001	n.s.	
Other disorders							
Unipolar depression	7	11	1	n.s.	<.05	<.001	
Generalized anxiety	7	14	0	<.05	<.01	<.001	
Panic	1	9	0	<.01	n.s.	<.001	
Phobic	2	10	0	<.01	n.s.	<.001	

<sup>&</sup>lt;sup>a</sup>Fisher's exact test; criterion for significance: p<.05, one-tailed.

TABLE 2. Lifetime Occurrence of Obsessive-Compulsive Disorder and Tic Disorders in Parents and Siblings of 16 Patients With Tourette's Disorder, 16 Patients With Obsessive-Compulsive Disorder, and 16 Normal Control Subjects<sup>a</sup>

	Lifetime Occurrence								
Disorder		Probands With sorder (N=74)	Relatives of P Obsessive-Compulsi	Relatives of Contro Subjects (N=86)					
	N	%	N	%	N	%			
Obsessive-compulsive disorder Tourette's disorder Any tic disorder	5 2 11	7 3 15 <sup>c</sup>	6 1 7	8 <sup>b</sup> 1 9 <sup>b</sup>	1 0 1	1 0 1			

<sup>&</sup>lt;sup>a</sup>The family history method, which is likely to provide underestimates, was used.

motor). Although one might imagine that tics would be more closely related to compulsions than to obsessions, the only patient with obsessive-compulsive disorder who reported obsessions in the absence of compulsions had a history of tic disorder. As in the patients with Tourette's disorder, the appearance of tics in the patients with obsessive-compulsive disorder generally preceded the development of the obsessive-compulsive disorder: for patients with obsessive-compulsive disorder with a tic disorder, the mean ±SD age at onset was 14.0±7.8 years for tics and 18.8±8.2 years for obsessions/compulsions. The types of tics reported by patients with obsessive-compulsive disorder included eye blinking, squinting, "snapping" the nose, humming, repeating words, throat clearing, and sniffing symptoms not unlike those of patients with Tourette's disorder (7), although less severe and of later onset. Three patients with obsessive-compulsive disorder reported that their tics persisted into the present, and three reported that they had abated.

As indicated in table 2, parents and siblings of probands with obsessive-compulsive disorder and probands with Tourette's disorder had significantly higher incidences of tic disorder than did relatives of control subjects, but they did not significantly differ from each other. Not shown in the table, three (13%) of the 24 relatives of probands with obsessive-compulsive disorder and a tic disorder had a tic disorder, compared with four (8%) of the 51 relatives of obsessive-compulsive disorder probands without a tic disorder, not a significant difference. Five (11%) of the 47 relatives of women with obsessive-compulsive disorder had a tic disorder, compared with two (7%) of the 28 relatives of men with obsessive-compulsive disorder, also not a significant difference. The tic symptoms in the relatives of patients with obsessive-compulsive disorder included eye blinking, squinting, head and neck jerking, tongue protrusion and biting, coughing, throat clearing, humming, and making noises. (The nephew of one patient with obsessive-compulsive dis-

<sup>&</sup>lt;sup>b</sup>Significantly higher than relatives of control subjects (p<.05, Fisher's exact test, one-tailed).

<sup>&#</sup>x27;Significantly higher than relatives of control subjects (p<.001, Fisher's exact test, one-tailed).

order had been given the diagnosis of Tourette's disorder at another center.)

Eleven patients with obsessive-compulsive disorder had either a tic disorder or a family history of tic disorder, compared with only one control subject (p<.001). Furthermore, the control subject with tics may have represented the "exception that proves the rule." This man, who reported an eye blinking tic when nervous, as did his father, spent 20 minutes a day checking the doors and windows of his home, a behavior that was not counted as a compulsion due to the absence of senselessness, resistance, or interference but that nevertheless stood out in contrast to the other control subjects.

#### Purpose and Volition

The criterion of purpose was examined as a means of distinguishing compulsions from tics. Nine patients with obsessive-compulsive disorder identified compulsions aimed at preventing some dreaded consequence, e.g., checking that the apartment building door was locked "so that a draft doesn't come in and give one of the old people pneumonia." However, seven patients with obsessive-compulsive disorder identified compulsions that were not related to the prevention of any dreaded consequence but were performed for vaguer reasons, e.g., repeatedly dressing and undressing "until I get the right feeling" or "the need to write down the thoughts in my mind." Those patients with obsessivecompulsive disorder whose compulsions were clearly purposeful were not immune to tics: of the six patients with obsessive-compulsive disorder with a positive history for tics, four reported typical compulsions designed to prevent the occurrence of dreaded consequences.

Sense of purpose was also not consistently absent in patients' reports of tics. Although prevention was generally not reported as a subjective motive behind tics, one Tourette's disorder patient stated that she performed a jumping tic "in order to prevent something bad from happening to my family." Tics were often performed in a typically compulsive manner. For example, a Tourette's disorder patient was observed to sniff in five times and then sniff out five times in rapid succession. When asked about this, he responded "I do everything in fives." Several patients in both the Tourette's and obsessive-compulsive disorder groups identified in their eye-blinking or throat-clearing tics the purpose of ridding themselves of irritating sensations in the eyes or throat. Sensory precursors to tics were reported by 14 patients with Tourette's disorder. Ten patients with Tourette's disorder (five men and five women) reported behaviors that were designed to maintain a sense of right-left bodily symmetry. For example, one of these patients explained that if she accidentally brushed a tree with her right hand, she then needed to intentionally brush another tree with her left hand "in order to balance it." Four patients with obsessive-compulsive disorder (three men and one women) but no control subjects reported the same phenomenon.

The DSM-III characterization of tics as involuntary also did not appear to be universally applicable. A Tourette's disorder patient maintained, "My tics are not involuntary. I do it because I feel a tension in the area that I need to release." This opinion was sustained by several other patients with Tourette's disorder, but several of the patients with obsessive-compulsive disorder reported that their compulsions were outside their voluntary control. Patients were more likely to describe a mounting sense of tension before performing tics, as opposed to anxiety before performing compulsions, but this distinction did not uniformly apply.

#### Associated Symptoms

Pathological doubt, slowness, and depersonalization were significantly more common in patients with Tourette's disorder and patients with obsessive-compulsive disorder than in control subjects, but the frequency of these did not differ significantly between the Tourette's disorder and obsessive-compulsive disorder groups (table 1). A Tourette's disorder patient described her depersonalization as follows: "It was very scary. I'd be sitting there talking with you and I'd doubt that I was really there, or that you were really there, or that we were really in the world. Then I'd wonder, 'What's the world?' 'What's a human being?'" Another Tourette's disorder patient ascribed the performance of some of her tics to the need to reassure herself that she really existed.

Compulsive touching, self-destructive behaviors, echo phenomena, and childhood attention deficit were more common in the patients with Tourette's disorder than in the patients with obsessive-compulsive disorder but were shown by none of the control subjects. In the patients with Tourette's disorder, the self-destructive behaviors included biting mouth and fingers, gnashing and grinding teeth, pulling out chunks of hair, sticking a toothpick in the hand, and inching a foot into a running lawn mower.

#### Psychodynamics

Psychodynamic features commonly described in obsessive-compulsive disorder were sometimes evident in patients with Tourette's disorder. One Tourette's disorder patient demonstrated intellectualization and isolation of affect when, after making reference to a thought of killing himself, he qualified this by stating, "What I was really trying to do just now was get the structure of the sentence exactly. I wasn't really worried about killing myself." Another Tourette's disorder patient reported being troubled by thoughts of "having sex with my mother and sucking my father's rear end hole." He made long lists of things that he "didn't want to do," presented these lists to his parents, and asked that they punish him should he try to do them.

TABLE 3. Scores on Self-Administered Psychometric Tests of 16 Patients With Tourette's Dis	order, 16 Patients With Obsessive-Compulsive
Disorder, and 16 Normal Control Subjects	

								Di	fference Be	tween Gr	oups	
	Score Obsessive- Tourette's Compulsive			Control		Tourette's vs. Obsessive- Compulsive		Tourette's vs. Control		Obsessive- Compulsive vs. Control		
	Diso	rder	Diso		Subje	ects	t		t		t	
Test	Mean	SD	Mean	SD	Mean	SD	(df=30)	р	(df=30)	р	(df=30)	p
Maudsley Obsessive Compulsive												
Inventory	8.4	6.7	15.2	6.1	4.3	3.4	3.0	<.01	2.2	<.05	6.3	<.001
Eysenck Personality Inventory												
Neuroticism	14.0	4.6	15.6	4.1	6.8	4.0	1.1	n.s.	4.8	<.001	6.2	<.001
Extraversion	12.2	4.1	11.3	5.0	14.1	3.0	<1	n.s.	1.5	n.s.	1.9	n.s.
State-Trait Anxiety Inventory												
Trait anxiety	47.6	13.0	58.4	10.4	30.2	5.4	2.6	.01	5.0	<.001	9.7	<.001

Psychological factors were sometimes evident in the development of the tics themselves. One of the patients with Tourette's disorder had a dramatic punching tic in which he would vigorously extend his fist, sometimes to within inches of the interviewer's face. He described how this tic originated in a frustrated impulse to reach out and smear his girlfriend's makeup, which intensified at the time of their angry breakup and persisted long afterward.

#### Other Mental Disorders

The rates of affective disorders (all either unipolar major depressive or dysthymic) and generalized anxiety disorder among patients with Tourette's disorder and patients with obsessive-compulsive disorder (table 1) were well in excess of those reported for the general population (13, 14). A high rate of panic and phobic disorders significantly distinguished patients with obsessive-compulsive disorder from both patients with Tourette's disorder and control subjects. However, these lifetime incidences may have been underestimated more in the Tourette's disorder group than in the other two groups because of its lower mean age.

The results of the self-administered psychometric tests appear in table 3.

#### **DISCUSSION**

Design limitations in this study require discussion. Because subjects were not randomly ascertained, it is conceivable that the subjects who volunteered to participate were not typical of the general populations with Tourette's disorder or obsessive-compulsive disorder. However, the specific questions posed by the study were not communicated to subject candidates in advance, which rules out the possibility of intentional self-selection. The 63% incidence of obsessive-compulsive disorder in the subjects with Tourette's disorder studied here is reassuringly close to previously reported estimates, as is the 6% incidence of Tourette's disorder in the subjects with obsessive-compulsive

disorder. Systematic data on the incidence of other tic disorders in subjects with obsessive-compulsive disorder are not available for comparison with the data obtained here, but we can think of no reason why subjects with obsessive-compulsive disorder and tic disorders would have been more likely to volunteer for interview than subjects with obsessive-compulsive disorder without tic disorders.

Comparison of our family history data with data obtained from direct interviews of family members of subjects with Tourette's disorder (2) indicates that our sensitivity for obsessive-compulsive disorder and tic disorders in relatives was lower by more than 50%. The family history method has generally been found to have high specificity but low sensitivity (15). Accurate estimates of the rate of tic disorders in relatives of probands with obsessive-compulsive disorder compared with the rate in the general population are needed. Although a portion of the data was beyond subjective interpretation (e.g., documentation of a facial tic was found in the child psychiatry clinic records of one of the subjects with obsessive-compulsive disorder, and tics were directly observed in some other subjects), it is possible that expectations of the nonblind interviewer introduced bias into the findings. The results should therefore be regarded as tentative until they can be replicated in more elaborate studies incorporating (as far as possible) blind interview design as well as larger sample sizes, random ascertainment of probands, age matching of groups with Tourette's disorder and obsessive-compulsive disorder, and direct interviewing of family members.

In patients with both tics and compulsions, it was sometimes impossible to tell where one ended and the other began, supporting the notion of a symptomatic continuum from simple tic through complex tic to compulsion. Certain kinds of compulsive behavior, such as touching and symmetry behavior, occurred more often in Tourette's disorder than in obsessive-compulsive disorder. Rasmussen and Tsuang (6) observed "symmetry obsessions" in 36% of their patients with obsessive-compulsive disorder (including one with concomitant Tourette's disorder), finding them

(as did we) to be more common in men with obsessivecompulsive disorder. Schilder (3) suggested that the occurrence of symmetry symptoms in obsessive-compulsive disorder pointed to an organic etiology. Our patients with Tourette's disorder showed a high rate of pathological doubt and slowness, psychopathology generally understood to be obsessional. Depersonalization, whose role in obsessional disorders Janet (16, 17) emphasized, also figured prominently in the psychopathology of patients with Tourette's disorder. The patients with Tourette's disorder were more anxious, neurotic, and compulsive according to the self-administered psychometric tests than were the control subjects but did not score as high on these measures as did the patients with obsessive-compulsive disorder, a finding reported elsewhere (18).

The most novel results of this study pertain to the high rate of tic symptoms in the patients with obsessive-compulsive disorder and their relatives. In fact, tics were more useful in distinguishing relatives of patients with obsessive-compulsive disorder from relatives of control subjects than were obsessions or compulsions. Only a few patients with obsessive-compulsive disorder, however, shared the echo phenomena, self-destructive behavior, symmetry behavior, and history of childhood attention deficit found in a substantial number of the patients with Tourette's disorder, and none had coprolalia.

The results suggest symptomatic overlap tending to blur the two disorders as well as symptomatic poles tending to distinguish them. With this pattern, the ease of differential diagnosis of a given patient would depend on his or her proximity to one of the poles. The arbitrary exclusion in *DSM-III* of the obsessive-compulsive disorder diagnosis in the presence of Tourette's disorder does not seem supportable. Pauls et al. (2) have presented data suggeting that the same genetic factor may be manifested as tics in some individuals and obsessions and compulsions in others, with penetrance in males weighted toward tics and penetrance in females toward obsessive-compulsive disorder (19). Our data are consistent with that formulation.

#### REFERENCES

 Green RC, Pitman RK: Tourette syndrome and obsessive compulsive disorder, in Obsessive-Compulsive Disorders: Theory

- and Management. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, Mass, PSG, 1986
- Pauls DL, Towbin KE, Leckman JF, et al: Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting an etiological relationship. Arch Gen Psychiatry 1986; 43: 1180–1182
- 3. Schilder P: The organic background of obsessions and compulsions. Am J Psychiatry 1938; 94:1397–1416
- Grimshaw L: Obsessional disorder and neurological illness. J Neurol Neurosurg Psychiatry 1964; 27:229–231
- Inouye E: Similar and dissimilar manifestations of obsessivecompulsive neurosis in monozygotic twins. Am J Psychiatry 1965; 121:1171–1175
- Rasmussen SA, Tsuang MT: Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 1986; 143:317–322
- 7. Shapiro AK, Shapiro ES, Bruun RD, et al: Gilles de la Tourette Syndrome. New York, Raven Press, 1978
- Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics and validity. Arch Gen Psychiatry 1981; 38:381–389
- Rachman SJ, Hodgson RJ: Obsessions and Compulsions. Englewood Cliffs, NJ, Prentice-Hall, 1980
- Eysenck HS, Eysenck SBG: Manual for the Eysenck Personality Inventory. San Diego, Educational and Industrial Testing Service, 1968
- Spielberger CD, Gorsuch RL, Lushene RE: Manual for the State-Trait Anxiety Inventory (Self-Evaluation Questionnaire). Palo Alto, Consulting Psychologists Press, 1970
- Rasmussen SA, Tsuang MT: Epidemiology and clinical features of obsessive-compulsive disorder, in Obsessive-Compulsive Disorders: Theory and Management. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, Mass, PSG, 1986
- Robins LN, Helzer JE, Weissman MM, et al: Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984; 41:949–958
- Weissman MM: The epidemiology of anxiety disorders: rates, risks, and familial patterns, in Anxiety and the Anxiety Disorders. Edited by Tuma AH, Maser J. Hillside, NJ. Lawrence Erlbaum Associates, 1985
- Weissman MM, Merikangas KR, John K, et al: Family-genetic studies of psychiatric disorders: developing technologies. Arch Gen Psychiatry 1986; 43:1104–1116
- Janet P. Les Obsessions et la Psychasthénie, vol I (1903). New York, Arno, 1976
- Pitman RK: Pierre Janet on obsessive-compulsive disorder (1903): review and commentary. Arch Gen Psychiatry 1987; 44:226–232
- Frankel M, Cummings JL, Robertson MM, et al: Obsessions and compulsions in Gilles de la Tourette's syndrome. Neurology 1986; 36:378–382
- Pauls DL, Leckman JF: The inheritance of Gilles de la Tourette's syndrome and associated behaviors: evidence for autosomal dominant transmission. N Engl J Med 1986; 315:993–997

# A 20-Month Follow-Up Study of 628 Women With Eating Disorders, I: Course and Severity

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A national sample of 628 women with eating disorders completed questionnaires in 1982 and again in 1984. According to initial simulated DSM-III diagnoses, 34 had anorexia nervosa with bulimic features, 392 had normal-weight bulimia, and 202 had a subdiagnostic eating disorder. Most respondents in the latter two groups met some criteria for alternative eating disorders. At follow-up, 29% of the anorexia nervosa group and 43% of the normal-weight bulimia group had improved enough to be classified as having a subdiagnostic disorder. Respondents who sought professional help between the initial survey and follow-up reported no more improvement than those who did not seek help.

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Over the past few years, a number of follow-up studies of patients with anorexia nervosa have been reported and critically reviewed (1–9). Among the important findings are the following: 1) about 30%-40% of all patients with anorexia nervosa recover totally, 2) about 40%-50% develop a bulimic syndrome although they may recover weight, and 3) the bulimic subtype of anorexia nervosa seems to have a worse prognosis than the restrictor subtype.

To date few follow-up studies of normal-weight bulimia have been published (10–12), so knowledge of the natural course of this syndrome is lacking. Russell's observation (13) that bulimia nervosa is a particularly "ominous" variant of anorexia nervosa led early students of the bulimic syndrome to be pessimistic about its course. However, most American researchers have studied so-called normal-weight bulimia as de-

fined in DSM-III—a syndrome that differs from Russell's "bulimia nervosa" in several respects, most importantly by not including features that are more like those of anorexia nervosa. Published follow-up reports on patients with normal-weight bulimia have, understandably, described small clinical samples, which are often treated by expert clinicians using their own different favored modalities. No information has been available on the natural history of the untreated syndrome. As Russell pointed out (14), such information is essential if we are to be able to assess the true effectiveness of treatment interventions.

This paper describes the course of eating disorder syndromes and symptoms in 628 women over an average interval of 20 months from 1982 to 1984. We intended to study whether these disorders in the community are best regarded as distinct diagnoses or as a continuum. Additionally, marked differences in help seeking permitted us to compare the course of those who had sought help for their disorders with the course of those who did not seek treatment.

#### **METHOD**

In response to an invitation in *Glamour* magazine in October 1982 for women with bulimic problems to participate in research, 1,729 women completed extensive mail-out questionnaires about their eating disorders (initial data) and also provided permission to be recontacted. A second mailing to this group in January 1984 yielded 692 responses (follow-up data). Comparison of data given by the women when they entered the study showed no statistically significant differences between responders and nonresponders to the follow-up questionnaire on variables concerning their eating disorders and demographic background.

Of the 692 follow-up responders, 628 completed both the initial and the follow-up questionnaire with sufficient information for us to determine simulated DSM-III eating disorder diagnoses at both time points. Although 661 responders provided sufficient information for an initial simulated diagnosis and 656 provided sufficient information for a follow-up simulated diagnosis, we restricted our analysis to those 628 respondents for whom we had complete data at both times.

Gayle E. Strauss, Cynthia Hatton, and Jonathan E. Yager assisted with the data analysis.

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Data reported in this paper were collected by means of the eating problems questionnaire developed by Johnson et al. (15) (to which we added questions to allow better approximation to DSM-III diagnoses), the Brief Symptom Inventory (a shortened form of the Hopkins Symptom Checklist) (16), the Eating Disorder Inventory (17), and a detailed questionnaire about help seeking. The Eating Disorder Inventory used at entry was an early version; the one used at follow-up was the final version of this instrument. For the two subscales (interoceptive awareness and maturity fears), which were not identical in the two versions, comparability was accomplished by using only identical items at the two time points and weighting subscale scores when there were different numbers of items.

We used the following criteria for our simulated DSM-III diagnosis of anorexia nervosa:

A. Intense fear of becoming obese, which does not diminish as weight loss progresses. Respondents had to give a rating of often, usually, or always to three separate items regarding their being "terrified of gaining weight," being "preoccupied with the desire to be thinner," and feeling "terrified of fat."

B. Disturbance of body image. Respondents had to endorse an item stating that they had "felt fat despite

others saying they were too thin."

C. A weight criterion. Present weight had to be 25% or more below the recommended mean weight for height according to the 1983 Metropolitan Life Insurance Company tables (18).

DSM-III criteria D ("refusal to maintain body weight over a minimal normal weight for age and height") and E ("no known physical illness that would account for the weight loss") were not used.

The following criteria were used for the simulated

DSM-III diagnosis of bulimia:

- A. Recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time, usually less than 2 hours). Respondents had to give a rating of often or always to two of the following items: I "eat a large amount of food during binges," "eat very rapidly during binges," "feel I can't stop during binges."
- B. Presence of at least three of five behaviors associated with bulimia.
- 1. Consumption of high-calorie, easily digested food during a binge. Respondents had to give a rating of always, usually, or often to each of these items: I "binge on bread/cereal/pasta," "binge on salty snack food," "binge on sweets."
- 2. Inconspicuous eating during a binge. Respondents had to give a rating of always, usually, or often to two statements: I "eat moderately in front of others and stuff myself when they are gone," "eat or drink in secrecy."
- secrecy."

  3. Termination of such eating episodes by abdominal pain, sleep, social interruption, or self-induced vomiting. Respondents had to endorse "I currently vomit after a binge."
  - 4. Repeated attempts to lose weight by severely

restrictive diets, self-induced vomiting, or use of cathartics or diuretics. Respondents had to endorse at least one of these: I "induce vomiting more than once a month," "take laxatives for weight control more than once a month."

- 5. Weight fluctuations of more than 10 lb. due to alternating binges and fasts. Respondents had to endorse My "weight goes up or down 10 pounds or more."
- C. Awareness that the eating pattern is abnormal and fear of not being able to eat normally. Respondents had to indicate that they currently "had a problem with bingeing" and give a rating of always, usually, or often to one of the following two items: I "feel I can't stop during a binge," "have gone on eating binges that I couldn't stop."
- D. Depressed mood and self-deprecating thoughts following eating binges. Respondents had to endorse two of the following three items: I "feel disgusted after a binge," "feel helpless after a binge," "feel guilty after a binge."
- E. Bulimic episodes not due to anorexia nervosa. While this is an arguable criterion, we established the diagnoses of anorexia nervosa and bulimia as separate from each other. Subjects were given a diagnosis of anorexia nervosa (which we called anorexia nervosa with bulimic features), normal-weight bulimia, or subdiagnostic eating disorder (not "subclinical," because the respondents did have symptoms).

In addition to making a diagnosis, we rated symptom severity. Two scales were constructed: a bulimic behavior scale and a psychosocial impact scale. The bulimic behavior scale measures the average frequency of binge eating, vomiting, and laxative abuse. The psychosocial impact scale assesses how much respondents' eating problems influence five areas: work, nonwork daily activities, thoughts, feelings about self, and personal relationships.

#### **RESULTS**

The 628 women completed the follow-up questionnaire a mean±SD of 1.74±1.12 years after the initial survey. Initially, their mean±SD age was 24.7±7.3 years, 34.1% were college graduates, 96.5% were Caucasian, 64.6% were single, 24.3% were married, and 11.1% were separated, divorced, or widowed. Differences among the diagnostic groups were few and not statistically significant: respondents who had anorexia nervosa with bulimic features were a bit younger, and this group included fewer college graduates. The mean±SD reported age at onset of the eating disorders was 14.9±5.8 years.

Respondents in the three diagnostic groups were of comparable height. Data for actual and desired weights initially and at follow-up are presented in table 1. Of the 34 respondents who initially met criteria for anorexia nervosa, 18 met *all* the criteria for bulimia. The average bulimia severity scores for the 16 who did

TABLE 1. Weight Changes Over 20 Months for 628 Women With Simulated DSM-III Diagnoses of Eating Disorders

	Reported Weight (lb.) <sup>a</sup>		Reported Weight as % of Standarda		Desired Weight (lb.) <sup>b</sup>		Desired Weight as % of Standard <sup>b</sup>	
Initial Diagnosis	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anorexia nervosa with								
bulimic features (N=34)								
Initial	94.2	8.2	71.1	5.0	95.4	11.1	71.6	6.5
Follow-up	103.9	17.2	78.4	12.1	99.9	13.5	75.4	9.2
Change:	+9.7 <sup>c</sup>	14.3	+7.4 <sup>c</sup>	10.5	+4.7	10.2	+3.6	7.6
Normal-weight								
bulimia (N=392)								
Initial	131.0	22.7	97.7	15.5	114.4	13.9	85.3	8.5
Follow-up	133.8	23.4	99.8	16.4	116.4	13.4	86.8	7.8
Change	+2.8°	13.7	+2.1 <sup>c</sup>	10.2	+2.1°	7.3	+1.6°	5.8
Subdiagnostic eating								
disorder (N=202)								
Initial	126.8	24.9	94.5	17.7	113.7	12.2	84.8	7.8
Follow-up	129.6	26.3	96.7	18.8	115.5	12.8	86.1	8.2
Change	+2.8°	14.1	+2.1°	10.4	+1.9°	5.8	+1.4 <sup>c</sup>	4.3

aSignificant difference between diagnostic groups in initial, follow-up, and change measures (p<.05, unbalanced ANOVA).

TABLE 2. Diagnoses at 20-Month Follow-Up of 628 Women With Simulated DSM-III Diagnoses of Eating Disorders at Initial Survey

	Diagnosis at Follow-Up								
Initial Diagnosis		Nervosa With Features		l-Weight imia	Subdiagnostic Eating Disorder				
	N	%	N	%	N	%			
Anorexia nervosa with bulimic features (N=34)	10	29.4	14	41.2	10	29.4			
Normal-weight bulimia (N=392)	4	1.0	220	56.1	168	42.9			
Subdiagnostic eating disorder (N=202)	1	0.5	66	32.7	135	66.8			
Total (N=628)	15	2.4	300	47.8	313	49.8			

not were nearly as high as those of the 18 who did, so for analysis all were considered as having anorexia nervosa with bulimic features. Initial weights for this group fell well under the criterion of 25% or more below standard weight (mean $\pm$ SD=94.2 $\pm$ 8.2 lb., 71.1%  $\pm$ 5.0% of standard weight). There was a significant increase in reported weights from initial survey to follow-up, with a mean $\pm$ SD of 9.7 $\pm$ 14.3 lb. for the group that had anorexia with bulimic features.

However, at follow-up, women who had anorexia nervosa with bulimic features desired to weigh less than their actual weights. In our experience, this very low desired weight signifies continued cognitive distortion of body image. Although reported weights for the groups with normal-weight bulimia and subdiagnostic eating disorders were at virtually the same percentage of standard weight for height initially and at follow-up, their *desired* weights were lower—13%—15% below standard—suggesting a certain degree of body image distortion for these groups as well.

This overlap of eating disorder diagnostic criteria among the three groups was also evident in the large percentages of respondents in each group who met *individual* diagnostic criteria for current anorexia nervosa and for bulimia. For example, more than 85% of the 594 respondents who did not have anorexia ner-

vosa had an intense fear of becoming obese (criterion A), while more than half met the criterion for body image distortion (criterion B).

Noteworthy, also, was the large proportion of respondents with subdiagnostic disorders who met individual criteria for the diagnosis of bulimia (44%—76%, depending on the criterion). Table 2 shows the changes in diagnostic patterns between initial and follow-up surveys. In general, respondents tended to become healthier.

Table 3 contains Eating Disorder Inventory scale scores for each diagnostic group initially and at follow-up. Scores for the groups that had anorexia nervosa with bulimic features and normal-weight bulimia closely paralleled scores published by Garner et al. (17) for clinical samples with anorexia nervosa and bulimia. Scores for the group with subdiagnostic eating disorders fell midway between Garner and associates' published norms for patients and for normal controls. These findings lend validity to our diagnostic groupings. In fact, on several scales our respondents scored higher than did the corresponding clinical samples of Garner et al. The group who had anorexia nervosa with bulimic features had the highest total scores and the highest scores on the drive for thinness, perfectionism, and interpersonal distrust subscales,

bSignificant difference between diagnostic groups in initial and follow-up measures (p<.05, unbalanced ANOVA).

cp<.05 (Student's t test for change scores not equal to 0).

TABLE 3. Eating Disorder Inventory Scale Scores at Initial Survey and at 20-Month Follow-Up for 628 Women With Simulated DSM-III Diagnoses of Eating Disorders

			Scor	e		
		lervosa With tures (N=34)	Normal Bulimia (		Subdiagno Disorder	
Eating Disorder Inventory Scale	Mean	SD	Mean	SD	Mean	SD
Drive for thinness						
Initial <sup>a</sup>	17.4	3.4	16.7	3.8	13.6	5.3
Follow-up <sup>a</sup>	14.6 <sup>b</sup>	5.2	13.9 <sup>b</sup>	5.6	11.7 <sup>b</sup>	6.3
Interoceptive awareness						
Initial <sup>à</sup>	14.6	8.0	11.0	6.9	8.3	6.0
Follow-up <sup>a</sup>	9.2 <sup>b</sup>	6.4	$8.0^{b}$	6.2	6.6 <sup>b</sup>	6.1
Bulimia						
Initial <sup>a</sup>	9.7	5.4	13.0	4.5	7.1	5.2
Follow-up <sup>a</sup>	7.2	5.7	8.7 <sup>b</sup>	5.8	6.0 <sup>b</sup>	5.7
Body dissatisfaction						
Initial <sup>a</sup>	16.8	8.5	19.7	6.6	16.2	7.6
Follow-up <sup>a</sup>	15.7	8.5	18.3 <sup>b</sup>	7.5	15.5	8.8
Ineffectiveness						
Initial <sup>a</sup>	12.9	8.3	11.1	7.5	7.1	6.3
Follow-up <sup>a</sup>	10.4	7.9	9.1 <sup>b</sup>	7.5	7.1	7.1
Maturity fears						
Initial <sup>a</sup>	6.7	6.9	4.5	5.5	3.6	5.1
Follow-up	4.7	3.7	5.0	3.9	4.4 <sup>b</sup>	3.5
Perfectionism						
Initial <sup>a</sup>	10.9	5.5	9.9	4.8	7.7	4.9
Follow-up <sup>a</sup>	10.9	5.7	8.7	5.0	7.3	4.9
Interpersonal distrust						
Initial <sup>a</sup>	8.1	5.5	6.1	4.8	4.9	4.3
Follow-up	5.4 <sup>b</sup>	4.2	4.8 <sup>b</sup>	4.6	4.2 <sup>b</sup>	4.5
Total inventory						
Initial <sup>a</sup>	97.1	31.0	92.1	26.8	68.6	27.4
Follow-up <sup>a</sup>	78.1 <sup>b</sup>	29.6	76.3 <sup>b</sup>	32.0	62.8 <sup>b</sup>	32.6

<sup>a</sup>p<.05 (unbalanced ANOVA for differences between diagnostic groups).

<sup>b</sup>p<.05 (Student's t test for change scores not equal to 0).

consistent with the overall clinical picture of the subtype. Differences among the diagnostic groups were significant; as expected, the subdiagnostic eating disorders group had the lowest scores. Body dissatisfaction scores were highest among the normal-weight bulimic subjects, consistent with their being farther than any other group from their desired body weights. With a few minor exceptions, scores on the Eating Disorder Inventory scales tended to improve from entry to follow-up.

Severity scores for bulimic behavior and psychosocial impact of symptoms initially and at follow-up are presented in table 4. Initially, the typical respondent who had anorexia nervosa with bulimic features binged somewhat more than once a week, the typical normal-weight bulimic subject binged midway between once a week and daily, and the typical subdiagnostic subject binged, on average, once a week. At follow-up, significant improvement was reported in binge eating, purging, and laxative use, ranging from 12.5% to 25.0% for the anorexia nervosa group and from 24.1% to 42.1% for the normal-weight bulimia and subdiagnostic disorders groups.

Psychosocial impact scale scores indicated that the typical anorexia nervosa and normal-weight bulimia respondent reported that her eating problems influenced her subjective state (thoughts and feelings about

self) between very much and totally; work, nonwork activities, and personal relationships were influenced between somewhat and very much. Subdiagnostic disorder respondents reported less negative impact. At follow-up, in contrast to the changes in bulimic behaviors we have described, very little change was reported in the total psychosocial impact scale scores, ranging from a mere 3.4% improvement for the group who had anorexia nervosa with bulimic features to a 6.7% worsening for the normal-weight bulimia group.

Finally, we examined the likelihood of improvement for each diagnostic group from initial survey to follow-up in relation to whether respondents had sought professional treatment in the community for eating disorders during that time. For the sample as a whole, 31.7% (N=199) had never sought any professional help, 53.8% (N=338) had sought help before the initial ratings in 1982, and 14.5% (N=91) had sought help only between entry into the study and follow-up. We excluded from the analysis all respondents who reported seeking help at or before entry. Adjusting for initial differences in severity between those who sought professional help and those who did not (by entering initial scores as a covariate), we found no outcome advantages in scores for weight, Eating Disorder Inventory scales, or severity scales for those who sought professional help between entry into the study and

TABLE 4. Changes Over 20 Months in Eating Disorder Severity Scale Scores of 628 Women With Simulated DSM-III Diagnoses of Eating Disorders

		exia Nervo c Features		Norm	al-Weight (N=392		Subdiagnostic Eating Disorder (N=202)		
	Sco	re	%	Sco	re	%	Sco	re	%
Severity Scale	Mean	SD	Change	Mean	SD	Change	Mean	SD	Change
Bulimic behavior (frequency) <sup>a</sup>									
Bingeing									
Bingeing Initial <sup>b</sup>	3.2	1.6		3.5	0.9		2.9	1.3	
Follow-up <sup>b</sup>	2.9	1.7		2.6	1.3		2.1	1.5	
Change <sup>b*</sup>			-12.5			$-25.7^{c}$			$-24.1^{\circ}$
Purging									
Initial <sup>b</sup>	3.2	1.9		2.4	1.8		2.0	1.9	
Follow-up <sup>b</sup>	2.5	2.1		1.8	1.7		1.6	1.7	
Change			$-25.0^{c}$			-29.2 <sup>c</sup>			$-25.0^{\circ}$
Laxative use									
Initial <sup>b</sup>	1.7	1.6		1.9	1.7		1.2	1.5	
Follow-up <sup>b</sup>	1.4	1.5		1.1	1.3		0.8	1.2	
Change	2	***	-23.5	***	*10	-42.1 <sup>c</sup>	0.0		-33.3°
Average of all three behaviors			2010			.2.,			0010
Initial <sup>b</sup>	2.7	1.1		2.6	0.9		2.0	1.1	
Follow-up <sup>b</sup>	2.1	1.2		1.8	1.0		1.5	1.1	
Change <sup>b</sup>	2.1	1.4	$-22.2^{c}$	1.0	1.0	-30.8°	1.5	1.1	$-25.0^{\circ}$
Psychosocial impact			Zer & 1 feet			50.0			25.0
(influence of eating problem) <sup>d</sup>									
Work									
Initial <sup>b</sup>	2.1	0.9		2,3	0.9		1.8	0.8	
Follow-up <sup>b</sup>	2.6	1.0		2.2	0.8		1.8	0.8	
Change	2.0	1.0	+28.6	2.2	0.0	-4.3	1.0	0.0	0.0
Nonwork daily activities			1 20.0			7.5			0.0
Initial <sup>b</sup>	2.9	0.7		2.8	0.8		2.3	0.8	
Follow-up <sup>b</sup>	2.9	1.0		2.6	0.8		2.3	0.8	
Change	2.7	1.0	-3.4	2.6	0.0	-7.1	2.4	0.0	0.0
Thoughts			-3.4			-7.1			0.0
Inoughts Initial <sup>b</sup>	3.4	0.6		3,4	0.6		2.9	0.8	
Follow-up <sup>b</sup>	3.3	0.8		3.4	0.6		2.9	0.8	
Change	3.3	0.0	-2.9	3.2	0.7	-8.8	2.9	0.0	0.0
Feelings about self			-2.9			-8.8			0.0
Initial <sup>b</sup>	3.3	0.7		3.6	0.5		2.7	0.8	
Follow-up <sup>b</sup>	3.3 3.4	0.7		3.3	0.3		3.2 3.1	0.8	
	3.4	0.0	+3.0	3.3	0.7	5.7	3.1	0.8	-3.1
Change			+3.0			-5.6			3.1
Personal relationships Initial <sup>b</sup>	2.6	0.0		2.0	0.0		2.4	0.0	
	2.6	0.8		2.9	0.8		2.4	0.9	
Follow-up <sup>b</sup>	2.9	0.8		2.8	0.8	2.4	2.4	0.9	4.0
Change			+7.7			-3.4			-4.2
Average of all five areas	2.0	0.5		2.0	0.6		2.4	0.6	
Initial <sup>b</sup>	2.9	0.5		3.0	0.6		2.6	0.6	
Follow-up <sup>b</sup>	3.0	0.7	. 2.4	2.8	0.6		2.5	0.7	0.0
Change			+3.4			-6.7			0.0

and all; 1=once a month or less; 2=a few times a month; 3=at least once a week; 4=daily; 5=more than once a day.

d1=none at all; 2=some; 3=very much; 4=total.

follow-up compared to the respondents who were never treated.

#### **DISCUSSION**

Several limitations of this study should be made clear. First, the respondents were not a carefully developed epidemiological sample but were a sample of convenience, to be regarded as a clinical sample: they were self-referred and self-motivated to participate; therefore, these findings cannot be readily generalized.

Second, we were unable to obtain follow-up data on large numbers of the initial sample, and we have no way of knowing whether those who did not respond at follow-up would have been more or less likely to improve than the responders. Of course, some may have died.

Third, our diagnostic simulations were at best approximations of *DSM-III* diagnoses, which cannot be substituted for in-depth clinical studies.

Overall, our findings raise serious questions about the categorical distinctiveness of current diagnostic labels; they are most consistent with a continuum

<sup>&</sup>lt;sup>b</sup>p<.05 (unbalanced ANOVA for differences between diagnostic groups).

cp<.05 (Student's t test for change scores not equal to 0).

model of the eating disorders, particularly those in which bulimic behaviors are present (19). The notion of a continuum is supported by the following findings: individual diagnostic criteria overlapped considerably among groups, they were prevalent in subdiagnostic respondents, and the tendency toward improvement (as measured by falling percentages of those who met the individual criteria) was consistent across groups. Our data suggest a continuum of weight preoccupation disorders, which start subclinically with large numbers of culturally influenced women who are preoccupied with their weight. In this view, as additional psychopathological and/or physiological burdens are superimposed on basic preoccupation with weight, we would expect to see, first, women who develop subdiagnostic eating disorders, then a more severely impaired group with so-called normal-weight bulimia, and then a still more severely ill group who have anorexia nervosa with or without bulimic features.

We found a general tendency toward improvement in these disorders, with some waxing and waning of symptoms. No one became entirely free of symptoms. The group that had the worst prognosis, consistent with Russell's observations, was the group with anorexia nervosa with bulimic features. In our 20-month follow-up period, improvement in that group tended to bring the respondents into the normal-weight bulimia category, whereas normal-weight bulimic subjects tended to improve enough to move into the subdiagnostic category. Although substantial improvement was reported for the bulimic behaviors of binge eating, purging, and laxative use, none was reported for the impact of these behaviors on various subjective and objective aspects of everyday life. Perhaps this indicates a time lag necessary for subjective changes to occur after behavioral changes; or the amount of behavioral change may simply not have been sufficient to generate a shift in subjective appraisal of the negative impact of these behaviors.

The finding that those who previously sought treatment in the community did no better than those who had never sought treatment should not be taken to indicate that specific treatments are ineffective for eating disorders. The "treatment" reported here was extremely heterogeneous, consisting of all sorts of psychotherapies and some pharmacotherapies provided by many kinds of practitioners. Those who sought treatment may have had more severe concurrent personality or affective disturbances, perhaps adding to the intractability of their eating disorders and tending to give them a worse prognosis than that of the untreated group. In addition, the untreated group may

have had greater denial, skewing their self-reports toward optimism. Further studies are required to clarify these issues.

#### REFERENCES

- 1. Morgan HG, Russell GFM: Value of family background and clinical features as predictors of long-term outcome in anorexia nervosa: four-year follow-up study of 41 patients. Psychol Med 1975; 5:355–371
- Stonehill E, Crisp A: Psychoneurotic characteristics of patients with anorexia nervosa before and after treatment and at follow-up 4-7 years later. J Psychosom Res 1977; 21:187-193
- 3. Sturzenberger S, Cantwell DP, Burroughs J, et al: A follow-up study of adolescent psychiatric inpatients with anorexia nervosa: the assessment of outcome. J Am Acad Child Psychiatry 1977; 16:703–715
- Casper RC, Eckert ED, Halmi KA, et al: Bulimia: its incidence and clinical importance in patients with anorexia nervosa. Arch Gen Psychiatry 1980; 37:1030–1034
- Garfinkel PE, Moldofsky H, Garner DM: The heterogeneity of anorexia nervosa: bulimia as a distinct subgroup. Arch Gen Psychiatry 1980; 37:1036–1040
- Hsu LKG: Outcome of anorexia nervosa. Arch Gen Psychiatry 1980; 37:1041–1046
- Hall A, Slim E, Hawker F, et al: Anorexia nervosa: long-term outcome in 50 female patients. Br J Psychiatry 1984; 145:407– 413
- Nussbaum M, Shenker IR, Baird D, et al: Follow-up investigation in patients with anorexia nervosa. J Pediatr 1985; 106: 835-840
- Tolstrup K, Brinch M, Isager T, et al: Long-term outcome of 151 cases of anorexia nervosa. Acta Psychiatr Scand 1985; 71: 380–387
- Lacey JH: Bulimia nervosa, binge eating and psychogenic vomiting: a controlled treatment study and long-term outcome. Br Med J 1983; 286:1609–1613
- 11. Pope HG, Hudson JI, Jonas JM, et al: Antidepressant treatment of bulimia: a two-year follow-up study. J Clin Psychopharmacol 1985; 5:320–327
- 12. Norman D, Herzog D, Chauncey S: A one-year outcome study in bulimia: psychological and eating symptom changes in a treatment and non-treatment group. Int J Eating Disorders 1986: 5:47–57
- 13. Russell GFM: Bulimia nervosa: an ominous variant of anorexia nervosa. Psychol Med 1979; 9:429–448
- Russell GFM: General management of anorexia nervosa and difficulties in assessing the efficacy of treatment, in Anorexia Nervosa. Edited by Vigersky RA. New York, Raven Press, 1977
- 15. Johnson CL, Stuckey MK, Lewis LD, et al. Bulimia: a descriptive survey of 316 cases. Int J Eating Disorders 1982; 2(1):3–16
- Derogatis LR, Lipman RS, Rickels K, et al: The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974; 19:1-14
- 17. Garner DM, Olmsted MP, Polivy J: Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. Int J Eating Disorders 1983; 2(2): 15–34
- Metropolitan Life Insurance Company: 1983 Metropolitan height and weight tables. Stat Bull Metrop Insur Co 1983; 64: 2–9
- 19. Garner DM, Garfinkel PE, O'Shaughnessy M: The validity of the distinction between bulimia with and without anorexia nervosa. Am J Psychiatry 1985; 142:581–587

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## Stressful Life Events and the Onset of a Generalized Anxiety Syndrome

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In a study of 2,902 subjects from the National Institute of Mental Health Epidemiologic Catchment Area Project in North Carolina, the association between life events and the onset of new cases of generalized anxiety syndrome varied across demographic subgroups and type of life event measure. Men reporting four or more life events had a risk of generalized anxiety syndrome 8.5 times that of men reporting zero to three life events; no association was found for women. Both men and women reporting one or more unexpected, negative, very important life events had a threefold increase in the risk of developing generalized anxiety syndrome. (Am J Psychiatry 1987; 144:1178–1183)

A lthough its definition will significantly affect its prevalence, generalized anxiety is one of the more common psychiatric problems. For example, Dunn (1) found anxiety neurosis to be the most common psychiatric disorder diagnosed by general practitioners in Britain. In a community survey, Lader (2) reported that 44% of the subjects experienced some anxiety symptoms, 31% could be classified as having a subclinical neurosis, and 5% suffered enough from severe anxiety to seek treatment. Similar to Lader's treatment-seeking group, we found an overall prevalence rate of about 8% (3) for generalized anxiety as defined by DSM-III and assessed by the Diagnostic Interview Schedule (DIS) (4).

Inherent within those theories which drive the research of anxiety is an association between the symptoms of the disorder and stressful events, as illustrated by the "fight-or-flight response" described by Cannon (5). The "learned fear" of experimental psychology (6) and the "stimulus-dependent" theory of anxiety (7) also suggest that the development of the disorder is in some way related to environmental stress. Nevertheless, most studies of stressful life events have concentrated on depressive syndromes as opposed to generalized anxiety (8).

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Two factors may explain the relative neglect of studies determining the impact of life events on generalized anxiety disorders. First, the syndrome is not well defined. No single symptom appears to be pathognomonic, and the experience of anxiety is so ubiquitous that the boundaries of the syndrome are often blurred. Second, the response of anxiety to the experience of a stressful life event is usually considered to be transient, immediately following the occurrence of the event. Thus, in typical retrospective studies, the causal relationship between events and the experience of anxiety is difficult to establish if immediate and transient anxiety is the only anxiety syndrome associated with stressful life events.

Despite these inadequacies, Barrett (9) found in 53 symptomatic community volunteers that the quality of life events differentiated depressive disorders from anxiety disorders. Events involving performance were experienced as more stressful by those with anxiety disorders, whereas exit events (events resulting in losses for the subjects) were experienced as more stressful by individuals suffering from depressive disorders. Of significance is that stressful life events may generate anxiety disorders of longer than transient duration.

In this retrospective study, the impact of life events on the development of a generalized anxiety syndrome was examined by using data from the Piedmont Health Survey (part of the National Institutes of Mental Health [NIMH] Epidemiologic Catchment Area Program), a longitudinal community survey of nearly 4,000 subjects in the Piedmont of North Carolina. A series of potentially stressful life events and qualities of these events were assessed during the first interview of this panel of subjects. One year later the subjects were reinterviewed, and during this second interview the symptoms of a generalized anxiety disorder were assessed. We hypothesized that respondents experiencing several life events (four or more), as well as those experiencing events perceived as unexpected, negative, and very important, would develop generalized anxiety. We expected the relative risk to vary by sex.

#### **METHOD**

Results are derived from the NIMH Epidemiologic Catchment Area Program. Five sites geographically

distributed throughout the continental United States (Greater New Haven, East Baltimore, Greater St. Louis, the Piedmont of North Carolina, and East Los Angeles-Venice) were each randomly sampled to yield 3,000 interviews, one per household, in the respective communities. In the Piedmont Health Survey, a sample was drawn to yield an additional 900 interviews from elderly (age 60 and older) community residents. The sampling strategy is presented in greater detail elsewhere (3).

In the wave I survey administered in 1982–1983, 3,922 subjects were interviewed (a 79% response rate). One year later, 2,993 subjects were reinterviewed (wave II). Although the survey included both community and institutional residents, this paper reports results from community respondents only. Complete information was available on life events at the first interview and generalized anxiety at the second interview for 2,902 respondents. Data were weighted in this study to distribute the attrition due to nonresponse (subjects who refused to participate, moved beyond the tracking range, or were unlocatable) evenly across the demographic subgroups, i.e., sex, race, age, and residence. For significance testing, the numbers were "downweighted" to the original wave II number of respondents.

Each participant in the survey underwent approximately a 2-hour interview, which included the DIS (4). The generalized anxiety section of the DIS, used only at wave II of the survey, screens for a series of symptoms associated with generalized anxiety. Symptoms from three of four categories—motor tension, autonomic hyperactivity, vigilance and scanning, and apprehensive expectation—lasting for 1 month or more compose the DSM-III criteria for the diagnosis. This article reports on those cases of generalized anxiety which developed within the year between the wave I and wave II interviews.

Because the DSM-III criteria for generalized anxiety disorder were changed in DSM-III-R, we have elected to use the term "generalized anxiety syndrome" to identify those individuals who report symptoms of a generalized anxiety disorder on the DIS that correspond to current DSM-III criteria. DSM-III-R criteria were not available at the time these data were collected. We also elicited information on other diagnoses considered in this study—panic disorder, obsessive-compulsive disorder, dysthymia, and major depression—in order to determine their 6-month prevalence at both wave I and wave II.

In the wave I interview, respondents were asked whether or not they had experienced each of 19 life events during the preceding 12 months. The events represented a number of different domains: parenthood, personal health, family health, legal matters involving self or family, and change in residence, work status, marital status, household composition, and financial status. The items included were those which had been found to be predictive of health outcome in earlier studies and covered events known to or at least

assumed to vary in their effects on the respondents. An expanded discussion of item selection is presented elsewhere (10). If an event was reported as occurring at least once during the previous year, respondents were asked to state whether the event (or the most important one if multiple events of the same type occurred) was "unexpected," "partially expected," or "expected"; whether the event had a "negative," a "neutral/mixed," or a "positive" effect on them; and if they considered the event's effect on their lives "very important," "somewhat important," or "not important."

The life event measures were scaled in the following two ways to estimate their impact on the development of a generalized anxiety syndrome: total of 19 life events reported and total of unexpected, negative, very important events reported. The total life events measure was dichotomized (0-3, 4+ events). Eleven percent of the men and 10% of the women reported that four or more events had occurred within the 12 months preceding the initial interview. The second life event measure was also dichotomized (0, 1+ events). Thirteen percent of the men and 16% of the women reported that at least one unexpected, negative, very important life event had occurred during the same time period. The traditionally used weighted measure developed by Holmes and Rahe (11) was found to be virtually identical to a simple summation of total events.

Mantel-Haenszel chi-square statistics were used to assess the strength and significance of the relationships. Summary statistics from the Statistical Analysis Systems statistical package (12) were also used. These statistics, which adjust for multiple strata across demographic subgroups, included the Cochran-Mantel-Haenszel and the Breslow-Day statistics.

#### **RESULTS**

Of the 1,602 women in the study, 56% were age 18–44 years, 62% were white, 65% had completed 12 or more years of education, and 53% lived in the one urban county. Of the 1,300 men, 63% were under 45 years of age, 66% were white, 63% had completed 12 or more years of education, and 56% lived in the urban area. These percentages are weighted to distribute the attrited cases across the demographic categories.

Sixty-five new cases of generalized anxiety syndrome were reported to have occurred within the year between the wave I and the wave II surveys. As shown in table 1, these new cases of generalized anxiety syndrome were more common in younger women, black men, and men with less education. Marked urban/rural differences were not found.

The reader should be cautioned not to consider these "incident cases" for two reasons. First, generalized anxiety disorder was not assessed at the wave I interview; therefore, in those emergent "cases," subjects were not known to be absent of the symptoms of

TABLE 1. Association Between Relative Risk of New Cases of Generalized Anxiety Syndrome and Selected Demographic and Life Event Measures<sup>a</sup>

		zed Anxiety			$\chi^2$ (df=1)	
	Syn	drome			Cochran-	
Measure	New Cases	Relative Risk	Logit <sup>b</sup>	Mantel- Haenszel	Mantel- Haenszel <sup>c</sup>	Breslow- Day <sup>d</sup>
Women (N=1,602)						
Age (years)		2.21	2.00	5.55°	6.55 <sup>f</sup>	0.234
18-44	31					
≥45	11					
Race		1.55	1.89	2.15	7.08 <sup>f</sup>	1.22
White	22					
Black	21					
Education		0.54	1.21	2.98	0.61	14.74 <sup>g</sup>
<high school<="" td=""><td>10</td><td></td><td></td><td></td><td></td><td></td></high>	10					
≥High school	33					
Residence		0.90	1.06	0.11	0.067	0.83
Rural	19			*****		
Urban	24					
Total life events		1.63	3.81	1.38	$22.60^{g}$	8.45 <sup>f</sup>
Four or more	6		0.00	2000		3
Fewer than four	36					
Unexpected, negative, very important life events		2.93	3.22	12.79 <sup>g</sup>	23,49 <sup>g</sup>	0.242
One or more	15		·		20117	· ·
None	27					
Men $(N=1,300)$						
Age (years)		1.67	2.00	1.23	6.55 <sup>f</sup>	0.234
18-44	17	****	2.00	1140	0.00	O TAMES T
≥45	6					
Race	Ü	2.76	1.89	6.37°	7.08 <sup>f</sup>	1.22
White	10	2.70	1.07	0.57	7.00	1.22
Black	13					
Education	15	4.60	1.21	13.01 <sup>g</sup>	0.61	14.74 <sup>g</sup>
<high school<="" td=""><td>17</td><td>4.00</td><td>1.21</td><td>15.01</td><td>0.01</td><td>17.77</td></high>	17	4.00	1.21	15.01	0.01	17.77
≥High school	6					
Residence	0	1.44	1.06	0.79	0.067	0.83
Rural	12	****	1.00	0.77	0.007	0.05
Urban	11					
Total life events	**	8.50	3.81	38.65 <sup>g</sup>	22.60 <sup>g</sup>	8.45 <sup>f</sup>
Four or more	12	0.50	3.01	30.05	22.00	0.43
Fewer than four	11					
Unexpected, negative, very important life events	11	3.85	3.22	11.35 <sup>g</sup>	23.49 <sup>g</sup>	0,242
One or more	8	5.05	ا الكاملات الكاملات	11.55	20.T/	0.474
None	15					

<sup>a</sup>Data are weighted.

<sup>c</sup>Stratum-adjusted Pearson chi-square statistic.

generalized anxiety syndrome at the time of the wave I interview (i.e., this was a retrospective assessment of new cases). Second, the *DSM-III* definition of generalized anxiety disorder has been changed in *DSM-III-R* but has not been tested clinically.

Table 1 also presents the estimated relative risk for the development of new cases of generalized anxiety syndrome for individuals at risk from the total life events and unexpected, negative, very important life events measures described earlier. An association between generalized anxiety syndrome and both life event measures was found. Men reporting four or more life events had a risk of generalized anxiety syndrome 8.5 times that of men reporting zero to three life events. By contrast, the association between total life events and generalized anxiety was not statistically significant for women. Although male respondents reporting unexpected, negative, very important life events had a higher relative risk of generalized anxiety syndrome than female respondents, the difference was not statistically significant.

In subsequent analyses, these relative risk estimates for the two life event measures were stratified for men and women by age, race, education, and residence. All demographic variables examined were associated with total life events and new cases of generalized anxiety for the men but not for the women (see table 2). Among the men, the relative risk was higher for the

<sup>&</sup>lt;sup>b</sup>Common relative risk. Logit estimators use a correction of 0.5 in cells of table that contain 0.

dTest for homogeneity of odds ratio. Cells that contain a 0 are not included in the calculation of this statistic.

<sup>&</sup>lt;sup>c</sup>p≤.05.

<sup>&</sup>lt;sup>f</sup>p≤.01. <sup>g</sup>p≤.001.

TABLE 2. Association Between Relative Risk of Generalized Anxiety Syndrome Secondary to Multiple Life Events and Selected Demographic Measures<sup>2</sup>

		zed Anxiety			$\chi^2$ (df=1)	_
		Secondary to Life Events		Mantel-	Cochran- Mantel-	Breslow
Measure	New Cases	Relative Risk	Logit <sup>b</sup>	Haenszel	Haenszel <sup>c</sup>	Day <sup>d</sup>
Women (N=1,602)						Administra
Age (years)			3.53		17.17 <sup>e</sup>	10.75 <sup>f,g</sup>
18-44	6	1.55		1.05		10175
≥45	0	0.00		0.50		
Race			3.53		20.83 <sup>e</sup>	11.99 <sup>g,h</sup>
White	3	2.14		1.81	20,00	
Black	3 3	1.16		0.06		
Education			3.59		19.61 <sup>e</sup>	10.55 <sup>f,g</sup>
<high school<="" td=""><td>0</td><td>0.00</td><td></td><td>0.79</td><td></td><td></td></high>	0	0.00		0.79		
≥High school	6	1.95		2.47		
Residence			3.79		22,41 <sup>e</sup>	9.15 <sup>f,g</sup>
Rural	1	1.43		0.21		
Urban	1 5	1.71		1.14		
Men $(N=1,300)$						
Age (years)			3.53		17.17 <sup>e</sup>	10.75 <sup>f,g</sup>
18-44	9	7.37		23.49 <sup>e</sup>		
≥45	2	11.64		14.34 <sup>e</sup>		
Race			3.53		20.83 <sup>e</sup>	11.99 <sup>g,h</sup>
White	7	18.38		34.31 <sup>e</sup>		
Black	7 5	4.68		9.53 <sup>h</sup>		
Education			3.59		19.61 <sup>e</sup>	10.55 <sup>f,g</sup>
<high school<="" td=""><td>8</td><td>5.53</td><td></td><td>16.11<sup>e</sup></td><td></td><td></td></high>	8	5.53		16.11 <sup>e</sup>		
≥High school	4	18.05		22.19 <sup>e</sup>		
Residence			3.79		22.41 <sup>e</sup>	9.15 <sup>f,g</sup>
Rural	5	6.48		14.25 <sup>e</sup>		
Urban	7	11.82		25.77 <sup>e</sup>		

<sup>a</sup>Data are weighted.

<sup>b</sup>Common relative risk. Logit estimators use a correction of 0.5 in cells of table that contain 0.

<sup>c</sup>Stratum-adjusted Pearson chi-square statistic.

<sup>n</sup>p≤.01.

subjects who were older, white, more highly educated, and from the urban area.

Associations between unexpected, negative, very important life events and generalized anxiety (with sex and each of the other demographic variables controlled for) are shown in table 3. Results of the Breslow-Day chi-square test for homogeneity suggest that the associations for men and women were not significantly different. However, closer examination of the education and residence subgroups suggests sex differences that canceled one another out: men with less than a high school education and women with a high school or more education who reported one or more unexpected, negative, very important life events had a higher risk of generalized anxiety symptoms; urban women, and then rural men, had the highest relative risk of generalized anxiety. White men and women and all respondents less than 45 years of age who reported at least one unexpected, negative, very important event had a common relative risk 3.2 or more times greater than that of the other subjects of experiencing generalized anxiety symptoms within the year before the second interview.

One concern of the investigators was the potential overlap of the generalized anxiety syndrome with dysthymia, major depression, and the other anxiety disorders. If significant overlap existed, then the confidence in the generalized anxiety syndrome as distinct from these more established diagnostic categories would be in jeopardy. In addition, any etiological hypotheses must be tempered, given the blurred boundaries among the disorders. As noted earlier, 65 cases of generalized anxiety disorder were reported to have developed between wave I and wave II of the study. Approximately two-thirds of both men and women had the single diagnosis of generalized anxiety syndrome, whereas the other third had at least one other depressive and/or anxiety disorder that met DSM-III criteria. The prevalence of the other disorders at wave II was as follows: dysthymia (80 cases, or a prevalence of 2.8%), major depression (53 cases, 1.8%), obsessive-compulsive disorder (32 cases, 1.1%), agoraphobia (121 cases, 4.2%), panic disorder (12 cases, 0.4%), simple phobia (235 cases, 8.2%), and social phobia (56 cases, 2.0%). Of the subjects who had generalized anxiety syndrome, seven women

dTest for homogeneity of odds ratio. Cells that contain a 0 are not included in the calculation of this statistic.

 $p \le .001$ .  $p \le .05$ .

gdf=3.

TABLE 3. Association Between Relative Risk of Generalized Anxiety Syndrome Secondary to Unexpected, Negative, Very Important Life Events and Selected Demographic Measures<sup>a</sup>

		nxiety Syndrome			$\chi^2 (df=1)$			
Measure		expected, Negative, ant Life Events		Mantel-	Cochran- Mantel- Haenszel <sup>c</sup>	Breslow- Day <sup>d</sup>		
	New Cases	Relative Risk	Logit <sup>b</sup>	Haenszel				
Women (N=1,602)						,		
Age (years)			3.35		22.77 <sup>e</sup>	2.73 <sup>f</sup>		
18-44	14	3.72		15.88 <sup>e</sup>				
≥45	2	0.98		0.00				
Race			3.18		21.49 <sup>e</sup>	6.28 <sup>f</sup>		
White	8	3.57		9.42 <sup>e</sup>				
Black	8 8	2.22		3.35				
Education			3.19		21.14 <sup>e</sup>	2.18 <sup>f</sup>		
<high school<="" td=""><td>3</td><td>2.07</td><td></td><td>1.10</td><td></td><td></td></high>	3	2.07		1.10				
≥High school	13	3.27		12.65 <sup>e</sup>				
Residence		•	3.29		22.92 <sup>e</sup>	2.76 <sup>f</sup>		
Rural	5	1.61		0.82				
Urban	11	4.52		16.47 <sup>e</sup>				
Men (N=1,300)								
Age (years)			3.35		22.77 <sup>e</sup>	$2.73^{f}$		
18–44	6	3.78		7.95 <sup>g</sup>				
≥45	6 2	4.31		3.74				
Race			3.18		21.49 <sup>e</sup>	6.28 <sup>f</sup>		
White	6	11.07	****	21.27 <sup>e</sup>				
Black	2	1.39		0.23				
Education	_		3.19		21.14 <sup>e</sup>	2.18f		
<high school<="" td=""><td>8</td><td>4.30</td><td>****</td><td>10.97<sup>e</sup></td><td></td><td></td></high>	8	4.30	****	10.97 <sup>e</sup>				
≥High school	Õ	0.00		0.08				
Residence	3	V.00	3.29	····	22.92 <sup>e</sup>	$2.76^{f}$		
Rural	5	4.05	J.27	7.07 <sup>g</sup>	~~~~	<b></b> , 0		
Urban	5 3	3.31		3.45				

<sup>a</sup>Data are weighted.

<sup>c</sup>Stratum-adjusted Pearson chi-square statistic.

and no men also had dysthymia, nine women and three men had major depression, three women and no men had obsessive-compulsive disorder, one woman and five men had agoraphobia, no women or men had panic disorder, five women and five men had simple phobia, and four women and no men had social phobia. Wave I rates of comorbidity were even lower for each category. Thus, although there was overlap

between the depressive and anxiety disorders and new cases of generalized anxiety syndrome, it did not bias the results of the analyses.

#### DISCUSSION

In this study, life events—as defined by the total number of events and a more subjective measure, namely, unexpected, negative, very important events—were associated with the onset of a generalized anxiety syndrome in the year after the experience of the event. This longitudinal (although retrospective) assessment of the impact of stressful life events on the development of a syndrome of generalized anxiety is one of the first reports to demonstrate such a relationship. The

findings suggest that the means by which one scales life events has an appreciable impact on the predictive value of those events. That is, risk from events assessed by the respondent as negative, unexpected, and very important was different from the risk from the total number of reported events. Moreover, sex differences across other demographic subgroups were evident.

Despite the methodological limitations, this study took advantage of a number of factors not readily available in other studies of etiologic associations between life events and anxiety. First, the use of a community sample as opposed to volunteers or a clinical sample provided an opportunity to eliminate the bias of self-selected respondents as well as the ability to control important demographic factors. The longitudinal design permitted the investigators to minimize the bias of increased recall of stressful life events given appreciable symptoms at the time of the interview. In addition, the consideration of the occurrence of events and their perceived valence, importance, and whether they were expected or unexpected allowed the investigators to compare a subjective measure of life event impact with the simple count of events. Finally, the size of the sample and the stringent

<sup>&</sup>lt;sup>b</sup>Common relative risk. Logit estimators use a correction of 0.5 in cells of table that contain 0.

<sup>&</sup>lt;sup>d</sup>Test for homogeneity of odds ratio. Cells that contain a 0 are not included in the calculation of this statistic.

 $p \le .001$ . fdf = 3.

<sup>&</sup>lt;sup>r</sup>df=3. <sup>g</sup>p≤.01.

approach to drawing the sample permitted population estimates.

There were, however, disadvantages in this study that only future investigations can overcome. First, it is not a true prospective study, in that anxiety symptoms were not screened at the first interview. Second, the DSM-III category of generalized anxiety disorder has already been considered "too inclusive" and therefore may not stand the test of clinical experience (13). At the time of this survey, however, the DSM-III category of generalized anxiety disorder was the best criterion available. The investigators were also concerned about the overlap of the symptoms of anxiety and depression. As noted in the results, generalized anxiety syndrome did not overlap appreciably with either dysthymic disorder or major depression, but these diagnostic categories are quite restrictive.

Inherent in studies of stressful life events is the impossibility of assessing the impact of ongoing environmental stress. Events, by definition, are self-limited, and one would expect to recover from the impact of these events. To understand the true relationship between environmental stress and generalized anxiety, persistent environmental stress must be taken into account. These analyses also do not account for those "vulnerability factors" (e.g., social support) which may mediate the effect of life events on the development of generalized anxiety syndrome. Finally, it could not be determined, from this analysis, if generalized anxiety syndrome occurred as an immediate aftermath of the life event or many months afterward. Almost by definition, the response of anxiety to the development of a stressful life event should occur within a short period of time following that event. On the other hand, a ripple effect could occur.

With increasing emphasis placed on the biological etiology of the symptoms of anxiety (14), the importance of environmental factors in the onset of anxiety syndromes must not be overlooked nor underestimated. This is especially true in the broad and residual category of generalized anxiety, in contrast to more discrete disorders such as agoraphobia and panic attacks.

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#### REFERENCES

- Dunn G: Longitudinal records of anxiety and depression in general practice: the second national morbidity survey. Psychol Med 1983; 13:897–906
- Lader M: The nature of clinical anxiety in modern society, in Stress and Anxiety, vol I. Edited by Spielberger CD, Sarason IG. New York, Halsted Press, 1975
- George LK, Hughes DC, Blazer DG: Urban/rural differences in the prevalence of anxiety disorders. Am J Soc Psychiatry 1986; 6:249-258
- Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981; 38:381–389
- Cannon WB: Neural organization for emotional expression, in Feelings and Emotions: The Wittenberg Symposium. Ldited by Regmert ML. Worcester, Mass, Clark University Press, 1928
- Seligman M, Johnson J: A cognitive theory of avoidance learning, in Contemporary Approaches to Conditioning and Learning. Edited by McGuigan FJ, Lumsden DB. New York, Halsted Press, 1973
- 7. Curtis GC: Anxiety and anxiety disorders: toward a conceptual reorientation. Psychiatr Clin North Am 1985; 8:159–168
- Brown G, Harris T: Social Origins of Depression: The Study of Psychiatric Disorder in Women. London, Tavistock Publications, 1978
- Barrett J: Psychiatric diagnoses (Research Diagnostic Criteria) in symptomatic volunteers. Arch Gen Psychiatry 1981; 38:153– 157
- Hughes DC, George LK, Blazer DG: Age differences in life event qualities: multivariate controlled analyses. J Community Psychol (in press)
- 11. Holmes TH, Rahe RH: The Social Readjustment Rating Scale.
  J Psychosom Res 1967; 11:213-218
- SAS Institute: SAS User's Guide: Statistics, 5th ed. Cary, NC, SAS Institute, 1985, pp 411

  –424
- Spitzer RL, Williams JBW: Diagnostic issues in the DSM-III classification of the anxiety disorders, in Psychiatry Lpdate: The American Psychiatric Association Annual Review, vol III. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1984
- Klein DF, Rabkin JG (eds): Anxiety: New Research and Changing Concepts. New York, Raven Press, 1981

# The South Oaks Gambling Screen (SOGS): A New Instrument for the Identification of Pathological Gamblers

Henry R. Lesieur, Ph.D., and Sheila B. Blume, M.D.

The South Oaks Gambling Screen is a 20-item questionnaire based on DSM-III criteria for pathological gambling. It may be self-administered or administered by nonprofessional or professional interviewers. A total of 1,616 subjects were involved in its development: 867 patients with diagnoses of substance abuse and pathological gambling, 213 members of Gamblers Anonymous, 384 university students, and 152 hospital employees. Independent validation by family members and counselors was obtained for the calibration sample, and internal consistency and test-retest reliability were established. The instrument correlates well with the criteria of the revised version of DSM-III (DSM-III-R). It offers a convenient means to screen clinical populations of alcoholics and drug abusers, as well as general populations, for pathological gambling. (Am J Psychiatry 1987; 144:1184-1188)

In 1980 APA included the diagnosis of pathological gambling under the category of disorders of impulse control in *DSM-III*. Both before and since that time, researchers have found evidence of pathological gambling among inpatients with diagnoses of alcohol and drug abuse (1–3); among probationers, parolees, and prisoners (unpublished 1985 paper by H.R. Lesieur and R.M. Klein); and among high school students (4).

According to the Commission on the Review of the National Policy Towards Gambling (5), there were an estimated 1.1 million "probable compulsive gamblers" in the United States in 1974. This is 0.77% of the adult population. In a critique of the commission's report, Nadler (6) placed the figures at anywhere from 1.1 to

4.4 million. In partial support of this critique, a survey of Ohio residents conducted for the Ohio Lottery Commission (7) estimated that 2.5% of the adult population were probable pathological gamblers and another 3.4% were potential pathological gamblers. In spite of these numbers, there are only about 10,000 members of Gamblers Anonymous and fewer than 20 treatment programs directed toward pathological gamblers in the United States today.

Pathological gambling is related to marital, financial, emotional, occupational, legal, and other problems. Separation and divorce, immense debts, depression and suicide, lost time at work and school, civil and criminal court appearances, suicide attempts by the gambler's spouse, and medical problems in the gambler are some of the problems that have been found to be associated with pathological gambling (8–12; unpublished papers by H.R. Lesieur and R.M. Klein [1985] and R.L. Custer and L.F. Custer [1978]).

Because of the severity of possible consequences, including suicide, early identification of pathological gamblers is important, yet many cases are currently overlooked in counseling, treatment, probation, parole, and other programs. A consistent, quantifiable, structured instrument that can be administered easily by nonprofessional as well as professional interviewers is needed. Such an instrument was constructed by the Gambling Treatment Team at South Oaks Hospital.

Two previous methods of identifying pathological gamblers are questions based on DSM-III criteria and the 20 questions of Gamblers Anonymous. The DSM-III criteria concentrate on late stage (desperation phase) signs and symptoms. They have been criticized (9) for being overly restrictive and for including criteria that show social class bias. Partially as a result of these critiques, the DSM-III criteria were revised by APA. The 20 questions of Gamblers Anonymous, which are based on the experience of Gamblers Anonymous members, have been used to screen patients at South Oaks Hospital and elsewhere. However, we have found that they generate an excessive number of false-negatives.

#### **METHOD**

Research was conducted in three stages. The first and second led to the development of the South Oaks

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The members of the Gambling Treatment Team at South Oaks, all of whom were involved in the research, included Dr. Blume; Richard Zoppa, M.D.; Robert Cahill, B.A., C.A.C.; Kay Maher, C.A.C.; Frank Casey, M.S.W., C.A.C.; Paul Burns, B.A., C.A.C.; Edna Bronzino, R.N.; Joyce Daly, B.A., C.A.C.; Mary Heineman, M.P.S., C.A.C.; Joseph Melman, M.S.W., M.P.A.; Jane Murphy; Mary Stark, C.A.C.; and Maurice Weiner, B.A.

Gambling Screen, and the third assessed its validity and reliability. The first two stages were conducted at South Oaks Hospital, a 105-year-old, 334-bed private psychiatric hospital located on the south shore of Long Island, N.Y. The hospital provides inpatient detoxification and rehabilitation for alcoholism and other drug dependencies and has an established program for the treatment of pathological gambling (13). The third stage involved four groups of subjects: members of Gamblers Anonymous who volunteered to complete the instrument while attending a national convention, a sample of university students, another control group of hospital employees, and a sample of patients at South Oaks.

During the first phase of the research, each inpatient with a diagnosis of alcohol or drug abuse who entered South Oaks from January 1 to September 30, 1984 (458 patients in all) was screened by using a Gambling History Test designed by the South Oaks Gambling Treatment Team. In addition, spouses and significant others of patients in treatment who visited the facility were asked about the patient's gambling habits.

The screening occurred in two steps. During the first week, while in the detoxification/orientation phase of treatment, patients were exposed to two lectures on gambling. The first lecture focused on switching addictions. Four days later, the patients saw a film entitled "You Bet Your Life," which was followed by a didactic presentation dealing with the disease concept of pathological gambling. The patients were given a questionnaire to complete after one of the lectures. They were told that even if the gambling they did was slight, infrequent, or "social," they were to answer all questions about gambling that applied to them. This questionnaire asked about their parents' as well as their own gambling habits. Every patient was interviewed by a counselor who reviewed the frequency of gambling, the amounts of money involved, the types of gambling, the gambling behavior (e.g., gambling to get even after losing, and drinking and gambling at the same time), as well as the patient's leisure time activities. If the patient denied any gambling, he or she was not interviewed further. If the patient admitted to gambling once a week or more, had a parent who gambled frequently, or bet more than \$10 on an event, a second interview was conducted by a counselor with extensive experience with gamblers as well as extensive training in alcohol studies. During the second interview patients were questioned intensively about family, job, financial, and other problems that might be associated with their gambling.

An index based on a modification of the DSM-III diagnostic criteria for pathological gambling was constructed. The index has seven components: 1) family disruption, 2) job disruption, 3) lying about gambling wins and losses, 4) default on debts, 5) going to someone to relieve a desperate financial situation produced by gambling, 6) borrowing from illegal sources, and 7) committing an illegal act to finance gambling.

A similar two-step process occurred in the inter-

views with significant others, except that they were asked about the degree of interest the patient demonstrated in various forms of gambling. Those who stated that the patient had a "heavy" or "obsessive" interest in gambling were interviewed further and questioned about family, job, financial, and other problems that may have been associated with the patient's gambling. The answers given by the patients and significant others were compared for consistency, and the patient was confronted with opposing evidence if inconsistencies surfaced.

In addition to the early screening, sometimes a gambling problem became evident during the hospital stay or in the process of outpatient aftercare. This has arisen in the course of group counseling, individual counseling, psychotherapy, or informal conversation. When this occurred, the patient was reinterviewed and the original gambling assessment form was corrected.

In addition to the Gambling History Test, counselors made independent assessments using a 5-point scale ranging from 1 (either one parent was a pathological gambler or the patient gambled heavily during the early or middle stages of alcohol or drug dependence but is not a pathological gambler) to 5 (patient has gambled extensively throughout his or her life and is definitely a pathological gambler). The results of the first stage were reported in an earlier paper (3).

In the second stage of the research process, counselors were consulted and questions were added to the survey instrument on the basis of their input. This was done to improve the congruence between counselor assessment and the screening test. A new schedule with 60 questions was devised. From December 1, 1984, to April 30, 1985, 297 inpatients with diagnoses of alcohol dependence, drug dependence, or pathological gambling were given the extended schedule. A new one-step procedure was created in an effort to shorten the time that it took for a counselor to conduct the interview. The inpatients were also screened by counselors and their status as pathological gamblers was reassessed on the basis of individual and group therapy sessions and interviews with their significant others.

After the second stage of the process, low-frequency items were eliminated, colinear items (r=.75 or higher) were extracted, and the resulting items were subjected to discriminant analysis by using the SPSSX computer program to further reduce their number. Counselor ratings used the 5-point scale described earlier in this paper. Since the rating of 3 was for subjects considered borderline, assessment scores of 4 or 5 were used as the discriminating variable. Twenty items were selected after this process. These 20 items constitute the South Oaks Gambling Screen (appendix 1).

To cross-validate the new index, stage three involved giving an anonymous questionnaire to 213 members of Gamblers Anonymous, 384 university students, and 152 hospital employees. The questionnaire was structured to include items from the proposed revision of *DSM-III* (*DSM-III-R*) as well as the 20-item South Oaks Gambling Screen.

#### RESULTS

#### Stages One and Two

A cross-check of the validity of the South Oaks Gambling Screen was made by cross-tabulating the patients' scores with the counselors' independent assessment scoring (r=.86, df=295, p<.001). A score of 5 or more, indicating five or more affirmative items on the South Oaks Gambling Screen, was chosen as an indication of probable pathological gambling to reduce the number of false-positive and false-negative codings. Of 297 inpatients, 214 received scores of 0, 44 received scores ranging from 1 to 4, and 39 received scores of 5 or more, placing them in the pathological gambling category. The counselors rated 261 of the patients as nonpathological gamblers and 36 as pathological gamblers. Six (2%) of the 261 nonpathological gamblers were erroneously placed in the pathological category (false-positives) by the index; three (8%) of the 36 pathological gamblers were erroneously placed in the nonpathological category (false-negatives).

An additional validity check was made by correlating the scores from family members' assessments of the existence or extent of a gambling problem with the patients' scores on the South Oaks Gambling Screen (r=.60, df=125, p<.001).

#### Stage Three

Using the cutting point of five or more positive responses on the South Oaks Gambling Screen, we found that 209 (98%) of 213 members of Gamblers Anonymous were classified as pathological gamblers (only 2% false-negatives). Twenty (5%) of the 384 college students were identified as pathological gamblers (tentatively classified as false-positives). Only two (1.3%) of the 152 hospital employees were identified as pathological gamblers. The South Oaks Gambling Screen proved to be capable of uncovering both male and female pathological gamblers. Twenty-one (95%) of the 22 female and 188 (98%) of the 191 male Gamblers Anonymous members showed up as pathological gamblers according to the cutoff score of 5.

As a further check on the validity of the data, scores on the DSM-III-R items were used to cross-check the South Oaks Gambling Screen. Using a score of four or more items on the DSM-III-R as an indication of probable pathological gambling, we found that 206 (97%) of the 213 Gamblers Anonymous members, 15 (4%) of the 384 college students, and one (1%) of the 152 hospital employees would be classified as pathological gamblers. Only four (2%) of the 213 subjects in the Gamblers Anonymous sample, 18 (5%) of the 384 subjects in the student sample, and one (1%) of the 152 subjects in the employee sample would have errors in classification as pathological or nonpathological gamblers. These data are presented in table 1. The South Oaks Gambling Screen and DSM-III-R are thus highly correlated (r=.94, df=747, p<.001).

TABLE 1. Agreement of DSM-III-R Diagnoses With South Oaks Gambling Screen Diagnoses of Pathological Gambling Among Gamblers Anonymous Members, Students, and Hospital Employees

DSM-III-R	Anon	nblers ymous (213)		dents =384)	Employees (N=152)		
Diagnoses	N	%	N	%	N	%	
True-positives	206	96.7	15	3.9	1	0.7	
True-negatives	3	1.4	351	91.4	150	98.7	
False-positives	3	1.4	5	1.3	1	0.7	
False-negatives	1	0.5	13	3.4	0	0.0	
Total errors	4	1.9	18	4.7	1	0.7	

To check the reliability of the instrument two alternative procedures were used. The 749 surveys were submitted to an internal consistency reliability check. The analysis showed that the screen is highly reliable (Cronbach's alpha=.97, p<.001). In addition, 74 inpatients and 38 outpatients at South Oaks filled out the questionnaire twice 30 or more days apart while in group sessions; 20 (18%) of these patients were pathological gamblers. The test-retest correlation (using a dichotomous classification of pathological or nonpathological) was .71 (df=110, p<.001). There was a tendency for scores to drop between test and retest. This was attributed to the patients' awareness that scores were being used in decisions about plans for inpatient treatment. The test-retest correlation was higher for outpatients (r=1.0, df=36, p<.001) than for inpatients (r=.61, df=72, p<.001).

#### **DISCUSSION**

The South Oaks Gambling Screen appears to be a valid, reliable screening instrument for the rapid screening of alcoholic, drug-dependent, and other patients for pathological gambling. This is important because previous studies of substance-abusing inpatients have shown clear connections between various forms of substance abuse and the presence of pathological gambling (1, 3, 14). Additional studies have found a connection between prison populations and pathological gambling (15; unpublished 1985 paper by H.R. Lesieur and R.M. Klein). There is clearly a need for an instrument that can screen patients, prisoners, and other populations for gambling problems.

The South Oaks Gambling Screen was recently adapted for use in an epidemiological survey by the New York State Office of Mental Health (unpublished 1986 paper by R.A. Volberg and H.J. Steadman). That study found that 1.4% of the adult population of New York had scores of 5 or higher on the South Oaks Gambling Screen and were therefore classified as probable pathological gamblers. This base rate for the general population is similar to that found in earlier studies (5, 7); however, the true sensitivity and specificity of the South Oaks Gambling Screen with the general population remains unknown. The extent to

which the sensitivity and specificity of this instrument may fluctuate in other populations (for example, general psychiatric and probation caseloads) is also undetermined. Differing base rates of pathological gambling in these populations may cause the false- and true- positive and negative rates to vary. Consequently, caution is advised until further testing has been conducted with these groups.

Current trends in treatment indicate that programs for pathological gamblers will continue to develop along the lines of already existing alcohol and drug treatment and at many of the same facilities. At present, alcohol- and drug-dependent inpatients and outpatients at South Oaks Hospital are screened by using the South Oaks Gambling Screen. In addition, spouses and significant others are screened to determine their assessment of patients' interest in different forms of gambling (from none to obsessive). This serves as a cross-check for patients who wish to conceal their gambling from the treatment staff. Wherever possible, this type of cross-checking should be used to augment the South Oaks Gambling Screen.

No other validated screening device is currently available that will screen patients for pathological gambling. The South Oaks Gambling Screen has the advantage of having been developed from the original DSM-III criteria and being highly correlated with DSM-III-R. In a sense, it provides a link between the two versions of the APA diagnostic criteria. The South Oaks Gambling Screen and screening guidelines are provided in appendix 1. It is our hope that this instrument will prove useful in improving identification, intervention, and treatment for the many pathological gamblers currently unrecognized by the organized health care and criminal justice systems.

#### REFERENCES

- Haberman PW: Drinking and other self-indulgences: complements or counter-attractions? Int J Addict 1969; 4:157–167
- Ingram-Smith N: Alcoholic rehabilitation centre of the West London Mission. Br J Addict 1967; 62:295–305
- Lesieur HR, Blume ŠB, Zoppa RM: Alcoholism, drug abuse, and gambling. Alcoholism: Clinical and Experimental Research 1986; 10:33–38
- 4. Lesieur HR, Klein RM: Pathological gambling among high school students. Addict Behav (in press)
- Commission on the Review of the National Policy Towards Gambling: Gambling in America. Washington, DC, US Government Printing Office, 1976
- Nadler LB: The epidemiology of pathological gambling: critique of existing research and alternative strategies. J Gambling Behavior 1985; 1:35–50
- 7. Culleton R: A Survey of Pathological Gamblers in the State of Ohio. Philadelphia, Transition Planning Associates, 1985
- 8. Lorenz VC, Shuttlesworth DE: The impact of pathological gambling on the spouse of the gambler. J Community Psychol 1983; 11:67-76
- Lesieur HR: The Chase: Career of the Compulsive Gambler. Cambridge, Mass, Schenkman, 1984
- McCormick RA, Russo AM, Ramirez LF, et al: Affective disorders among pathological gamblers seeking treatment. Am J Psychiatry 1984; 141:215–218
- 11. Lorenz VC, Yaffee R: Pathological gambling: psychosomatic,

- emotional and marital difficulties as reported by the gambler. J Gambling Behavior 1986; 2:40–49
- Greenberg HR: Psychology of gambling, in Comprehensive Textbook of Psychiatry, 3rd ed, vol 3. Edited by Kaplan HI, Freedman AM, Sadock BJ. Baltimore, Williams & Wilkins, 1980
- Blume SB: Treatment for the addictions: alcoholism, drug dependence and compulsive gambling in a psychiatric setting. J Subst Abuse Treat 1986; 3:131–133
- Ramirez LF, McCormick RA, Russo AM, et al: Patterns of substance abuse in pathological gamblers undergoing treatment. Addict Behav 1984; 8:425–428
- Royal College of Psychiatrists: Submission of Evidence to the Royal Commission on Gambling. London, Royal College of Psychiatrists, 1977

#### APPENDIX 1. The South Oaks Gambling Screen

1. Please indicate which of the following types of gambling you have done in your lifetime. For each type, mark one answer: "not at all," "less than once a week," or "once a week or more."

veek	or more	•"		
a. b.	Not at all	Less than once a week	Once a week or more	played cards for money bet on horses, dogs, or other animals (in off-track betting, at the track, or with a bookie)
c.		<u></u>		bet on sports (parlay cards, with a bookie, or at jai alai)
d.	···		- 1745	played dice games (including craps, over and under, or other dice games) for money
e.	****			went to casino (legal or otherwise)
f.				played the numbers or bet on lotteries
g. h.				played bingo played the stock and/or commodities market
i.		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		played slot machines, poker machines, or other gambling machines
j.				bowled, shot pool, played golf, or played some other game of skill for money
amb ——	led with never \$1 o more \$10	on any r have g r less than \$	one day ambled 1 up to	more than \$100 up to \$1,000 more than \$10,000 up to \$10,000 more than \$10,000
				e a gambling problem? mother gamble (or gambled)

my father gambles (or gambled) too much

\_ my mother gambles (or gambled) too much

neither one gambles (or gambled) too much

too much

### SOUTH OAKS GAMBLING SCREEN

4. When you gamble, how often do you go be to win back money you lost?	ack anoth	16. If you borrowed money to gamble or to pay gambling debts, who or where did you borrow from? (check "yes" or "no" for each)						
some of the time (less than half the	e time) I l	lost	•	n	0	ye	S	
most of the time I lost	•		a. from household money	(	)	(	)	
every time I lost			b. from your spouse	ì	í	ì	í	
every time I lost			c. from other relatives or in-laws	7	í	7	ί,	
5. Have you ever claimed to be winning mon	ev gambl	ing but		(	,	(	,	
weren't really? In fact, you lost?	-, 6		d. from banks, loan companies, or credit	,		,	,	
never (or never gamble)			unions	(	)	(	,	
			e. from credit cards	(	)	(	)	
yes, less than half the time I lost			f. from loan sharks (Shylocks)	(	)	(	)	
yes, most of the time			g. you cashed in stocks, bonds, or other					
C. Da was fast was been seen had a marklam		لاحسناط	securities	- (	)	1	)	
6. Do you feel you have ever had a problem	with gan	nonngr	h. you sold personal or family property	ì	í	ì	ń	
no			i. you borrowed on your checking	,	,	'	,	
yes, in the past, but not now				,	١.	,	,	
yes			account (passed bad checks)	(	)	(	)	
			j. you have (had) a credit line with a					
7. Did you ever gamble more than you			bookie	(	)	(	)	
intended to?			k. you have (had) a credit line with a					
	yes	no	casino	(	)	(	)	
	•			•	•	•	•	
8. Have people criticized your gambling?			Scoring					
	yes	no	50011119					
O Harra man falk andless about the man			Carres on the Carrel Cala Carreling C		. :	.16 .		
9. Have you ever felt guilty about the way			Scores on the South Oaks Gambling Sc					
you gamble or what happens when you			determined by adding up the number of ques	tions	tha	t sho	w	
gamble?			an "at risk" response:					
	yes	no	Questions 1, 2, and 3 are not counted.					
10 ITama man anan fala lilaa mina mani d lilaa						.:	. т	
10. Have you ever felt like you would like			Question 4: most of the time I lost,	or ev	very	time	: 1	
to stop gambling but didn't think you			lost					
could?			Question 5: yes, less than half the time	ie I l	ost,	or ye	es,	
	yes	no	most of the time					
11. Have you ever hidden betting slips,			Question 6: yes, in the past, but not a	now,	or y	res		
lottery tickets, gambling money, or other			Question 7: yes					
signs of gambling from your spouse,			Question 8: yes					
children, or other important people in			Question 9: yes					
your life?			Question 10: yes					
your me:								
	yes	no	Question 11: yes					
12. Have you ever argued with people			Question 12 not counted					
you live with over how you handle			Question 13: yes					
money?			Question 14: yes					
money:			Question 15: yes					
	yes	no	Question 16a: yes					
13. (If you answered yes to question 12):			Question 16b: yes					
Have money arguments ever centered on			Question 16c: yes					
your gambling?			Question 16d: yes					
your gamoinig:								
	yes	no	Question 16e: yes					
14. Have you ever borrowed from			Question 16f: yes					
someone and not paid them back as a			Question 16g: yes					
result of your gambling?			Question 16h: yes					
result of your gamoning:	1100	***	Question 16i: yes					
	yes	no	Questions 16j and 16k not counted					
15. Have you ever lost time from work								
(or school) due to gambling?			Total = $\underline{\hspace{1cm}}$ (20 questions are counted)					
(an outlook) may to market have	Vec	no	5 or more = probable pathological gambler					
	yes	110	5 of more - probable pathological gambler					

## The Washington University Sentence Completion Test Compared With Other Measures of Adult Ego Development

George E. Vaillant, M.D., and Leigh McCullough, Ph.D.

One hundred seven men who had been studied prospectively from age 18 to age 63 completed the Washington University Sentence Completion Test at age 55±2 years. Ego level as assessed by the Sentence Completion Test correlated significantly with psychosocial maturity, with number of psychiatric visits, and, perhaps, with creativity. Ego level as assessed by the Sentence Completion Test did not correlate with mental health, psychopathology, or maturity of defenses. The authors discuss possible reasons for these findings. (Am J Psychiatry 1987; 144:1189–1194)

This paper represents an effort to study levels of ego development as assessed by Loevinger and Wessler's Washington University Sentence Completion Test (1) and by a measure of maturity of defensive style (2, 3). A subordinate question posed is, What is the relative correlation of each of these different models of ego development with objectively measured mental health (4) and with adult psychosocial development assessed in conformity with Erikson's model (5)?

Of all developmental theories postulating that important facets of adult personality correspond to developmental stages, Loevinger's scheme for ego development (6, 7) has the best designed and most empirically based measure for its assessment (8). Loevinger's ego development theory is intended to be comprehensive and includes cognitive, social, psychosexual, and moral strands of development. Her model postulates a sequence of qualitatively distinct ego stages as an innate characteristic of human development. As in Piaget's system, she suggested that these stages make

up an invariant hierarchical order. Loevinger made no claim that ego development should be associated with mental health.

A second model of ego development (9) postulates that ego mechanisms of defense mature over time in a fashion parallel to but not identical with Kohlberg's (10) and Erikson's (5) schemes for adult moral and psychosocial development. This model stresses the high correlation of "maturity" of defenses with mental health (11, 12)—the implication being that ego maturity is as important for mental health as it is for other aspects of adult development. Although one of us (G.E.V.) (9) has hypothesized that a close correlation should exist between maturity of defensive style and ego level as defined by Loevinger, such an association has not been documented.

#### **METHOD**

Between 1940 and 1942 a university health service chose 204 male college sophomores for intensive multidisciplinary study (13). The men were selected because their freshman health service physical examination had revealed no mental or physical health problems and the college deans viewed the men as having the potential to become promising adults. By 1975 six men had withdrawn from the study and 18 had died. For nearly 40 years the remaining 180 men were followed prospectively by means of annual or biennial questionnaires. The present data, except when noted, are derived from these questionnaires. The men were also reinterviewed at age 25, at age 30, and again between age 47 and age 57.

With the exception of ratings for maturity of defensive style and psychosocial development, each of the sets of ratings described below was made by independent raters blind to the other ratings.

1. The Washington University Sentence Completion Test (1) was part of the 1975 questionnaire received by all surviving men in the sample at age  $55\pm2$  years. The Sentence Completion Test is a means of assessing ego level by asking subjects to complete 36 sentence stems. Each sentence answer is scored separately from all other sentence answers and is individually assigned to one of nine ego development levels by matching each sentence completion with response categories provided

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in a scoring manual. The strategy of scoring is to determine a total protocol rating of ego level based on an individual's score on the 36 sentence stems. All of the Sentence Completion Tests in our sample were scored by Loevinger's Washington University group, who were kept blind to all other ratings. The eight conventionally scored stages are 1) impulsive (I-2), 2) opportunistic (delta), 3) conformist (I-3), 4) conscientious/conformist (I-3/4), 5) conscientious (I-4), 6) individualistic (I-4/5), 7) autonomous (I-5), and 8) integrated (I-6). Methods, rationale, and reliability are described in detail elsewhere (1, 7, 8).

- 2. Maturity of defenses was assessed when the men were 46–48 years old. Two raters blind to the men's Sentence Completion Test ego level reviewed each man's entire case dossier in chronological order. Each dossier contains roughly 300 pages of data; these are in the form of autobiographical responses to biennial questionnaires, interview summaries, psychological tests, correspondence, etc. Examples of adaptive behavior at times of crisis and conflict were excerpted as vignettes. Approximately 20-30 vignettes were collected for each man. On the basis of a glossary (2, 14), these vignettes were classified whenever possible as belonging to one of 15 defense headings. These 15 defenses were grouped into three categories: 1) immature (schizoid fantasy, projection, passive aggression, hypochondriasis, acting out, and dissociation), 2) intermediate (intellectualization/isolation, repression, displacement, and reaction formation), and 3) mature (sublimation, suppression, anticipation, altruism, and humor). The average subject was noted to use three to eight different defenses. Rater reliability (r) for scaling maturity of defenses in this manner ranged from .72 to .84. Methods, rationale, and reliability are described in detail elsewhere (9, 12, 14).
- 3. Our measure of psychosocial development followed a slightly modified version of Erikson's own definitions of stages of life (5, 15) and is described elsewhere (16). At age 47-50 years the men were given a rating of 1-5: 1=identity not achieved (still dependent on family of origin), 2=identity but not intimacy achieved, 3=intimacy (Erikson's stage VI, defined by 10 or more years of gratifying marriage but not achievement of career consolidation), 4=career consolidation (defined by competence at, enjoyment of, and commitment to job but not achievement of generativity), and 5=generativity (Erikson's stage VII) achieved. Generativity was defined as demonstrating a clear capacity for "care," productivity, and establishing and guiding the next generation-especially sustained responsibility for fostering the well-being and development of young adults. Rater reliability (r) for psychosocial stage classification was .61.
- 4. Psychiatric visits indicated the number of postcollege visits to a psychiatrist or psychotherapist. This information was elicited in interviews and reported on several different questionnaires over a 40-year period.
- 5. Healthy adult adjustment, age 30 to age 47, was assessed at age  $47\pm2$  years on a 7-16-point scale. A

low score indicated healthy adjustment. The scale summed seven relatively objective longitudinally derived variables. Five variables were scored as 2 (true) or 1 (untrue). These variables were 1) little occupational advancement, 2) limited recreation with others, 3) less than 2 weeks of vacation taken, 4) more than 5 days of annual sick leave taken, 5) earned annual income less than \$20,000/year (1968 dollars). Two variables were scored as 3 (definite), 2 (ambiguous), or 1 (untrue); these were unhappy marriage and chronic job dissatisfaction. The qualifications, rationale, and point assignment are defined elsewhere (4). This scale correlated at r=.67 with the Health-Sickness Rating Scale of Luborsky (17).

- 6. Healthy adult adjustment, age 47 to age 62, was assessed on the basis of questionnaire data obtained during the previous 15 years. The men were rated for mental health again at these ages. The assignment of points was the same as it was for age 30 to age 47 except that three items were added: 1) global adjustment to aging (5 points), 2) psychiatric visits at age 48 to age 62 (2 points), and 3) use of tranquilizing medication (2 points). Early retirement (3 points) replaced the 2-point income criterion. The scores ranged from 10 to 27.
- 7. Childhood strengths were rated on a scale from 1 to 20 by two research assistants blind to all data gathered after the men were 19. This scale is described in detail elsewhere (18). A low score indicated childhood and emotional problems, a lack of family cohesion, and poor parental relations. Rater reliability (r) was .71.
- 8. Alcohol dependence was rated according to the criteria of the revised version of *DSM-III* (*DSM-III-R*). Like most other data in the study, this judgment was based on biennial questionnaires prospectively gathered over 40 years, supplemented by interview data and medical records. Virtually all of the men classified as alcohol dependent had four or more different alcohol-related problems on the Problem Drinking Scale (19).
- 9. Outstanding traits (13) were also assessed. At the end of their college career, a psychiatrist reviewed all of the data gathered on the men during the previous 3 years and assigned to each man several of 25 personality traits on a 1=absent and 2=present basis. Rater reliability was not determined. Of the 25 traits, only four were significantly associated with the Sentence Completion Test findings: 1) ideational—"likes to deal with ideas . . . to be theoretical or analytical . . . high verbal ability ... interested in scholarship, literary criticism, and social problems," 2) creative and intuitive—"characterized by high ability for self-expression ... original and creative in thought," 3) cultural— "enjoyment of participation in literature or the arts is predominant," and 4) inarticulate—"inability to express themselves in language ... their descriptions tend to be meager and matter-of-fact, particularly concerning their own personal feelings and experiences."

TABLE 1. Sentence Completion Test Ego Levels Among Six Groups of Normal Male Subjects

	14-Ye:	ar-Olds		6–25-Y		-	35–80-Y	'ear-Old		55-Year in This		**************************************
	Studied by Hauser et al. (20) (N=76)				College (N=162)		Veterans Studied by McCrae and Costa (22) (N=240)		Listed in Who's Who (N=21)		Total (N=107)	
Ego Level	N	%	N	%	N	%	N	%	N	%	N	%
Impulsive or opportunistic	27	36	94	30	26	16	10	4	0	0	0	0
Conformist	9	12	82	26	19	12	19	8	0	0	0	0
Conscientious/conformist	29	38	107	34	66	41	103	43	5	24	25	23
Conscientious	9	12	28	9	36	22	77	32	4	19	43	40
Individualistic	2	3	3	1	13	8	29	12	6	29	28	26
Autonomous	0	0	0	0	2	1	2	1	4	19	8	7
Integrated	0	0	0	0	0	0	0	0	2	10	3	3

TABLE 2. Correlations of Sentence Completion Test Ego Levels and Other Indexes of Mental Health for 107 Normal Men

	Correlation (r)									
Index of Mental Health <sup>a</sup>	Ego Level	Psychosocial Level	Adult Adjustment	Defense Maturity	Psychiatric Visits	Childhood Environment	Alcoholism by Age 62			
Psychosocial level at age 47 Healthy adult adjustment at	.22 <sup>b</sup>			-						
ages 30-47	04	.49 <sup>c</sup>								
Defense maturity at ages 20-47	.04	.28 <sup>d</sup>	.39°							
Number of psychiatric visits by										
age 62	$30^{e}$	.04	.34 <sup>c</sup>	.26 <sup>e</sup>						
Warm childhood environment	.08	.21 <sup>b</sup>	.26 <sup>e</sup>	.34°	.25e					
Alcoholism by age 62	08	.22 <sup>b</sup>	.19 <sup>b</sup>	.27 <sup>e</sup>	.28 <sup>c</sup>	.14				
Healthy adult adjustment at										
ages 47-62	09	.34 <sup>c</sup>	.53°	.49 <sup>c</sup>	.51°	.25 <sup>e</sup>	.22 <sup>b</sup>			

<sup>&</sup>lt;sup>a</sup>The scoring system was reversed so that a low numerical score indicated "healthy" or "mature" for all measures. Thus, a mature ego level, a low number of psychiatric visits, healthy adult adjustment, and no evidence of alcoholism received low scores.

<sup>b</sup>p<.05.

#### **RESULTS**

Only 107 men, roughly two-thirds of those eligible, returned scorable Sentence Completion Tests. Some of the men completed the rest of their 1975 questionnaire but refused to complete the Sentence Completion Test; others did not respond that year. Because a rich data set was available for all of the men in the sample, it was possible to say with some certainty that in most respects men who responded to the Sentence Completion Test did not differ significantly from nonresponders. The greatest source of bias between responders and nonresponders was that those who returned a completed Sentence Completion Test manifested a more mature defensive style ( $\chi^2=5.1$ , df=1, p<.05), were "ideational" in college (t=2.00, df=196, p<.05), and were more likely to have achieved career consolidation and generativity (t=2.37, df=184, p<.02).

Table 1 shows the distribution of the Sentence Completion Test ego development stages among six groups of normal male subjects of contrasting age and educational attainment. Age, advanced educational attainment, and, perhaps, higher socioeconomic status affected Sentence Completion Test ego level. At an average age of 55 and with a mean of 18–19 years of educational attainment, the men in our study showed the highest mean ego level that Loevinger's test has found thus far. It was of interest that the men in our study who were listed in Who's Who in America showed an even higher mean ego level, but the numbers are too small to be statistically significant.

Table 2 illustrates that many childhood strengths, psychosocial maturity at age 47, healthy adult adjustment at age 47 and age 62, and mature defenses at age 47 were all positively and significantly correlated with each other. Not surprisingly, all five variables were negatively correlated with alcohol dependence and with lifetime number of psychiatric visits. Surprisingly, ego level was correlated positively but not significantly with global maturity of defenses. Indeed, ego level was not significantly correlated with five of these seven highly intercorrelated measures of global mental health.

Ego level was significantly and positively correlated only with psychosocial development, which we predicted, and with lifetime number of psychiatric visits,

<sup>°</sup>p<.001.

 $<sup>^{</sup>d}$ p<.01; the strength of the correlation may be too high because psychosocial level and defense maturity were often assessed by the same rater.  $^{e}$ p<.01.

TABLE 3. Correlations of Sentence Completion Test Ego Level With Variables Consistent With Creativity and Psychological Mindedness in 107 Normal Men

	Corr	elation (r)
Variable	Mature Ego Level	Mental Health at Age 47
Inclusion in Who's Who at age 62	.25ª	.05
Use of sublimation at ages 19-47	.19	.05
Ideational trait at age 19	.22 <sup>b</sup> .22 <sup>b</sup>	12
Cultural trait at age 19	.22 <sup>b</sup>	$17^{\rm b}$
Creative and intuitive trait at		
age 19	.23 <sup>a</sup>	12
No visits to psychiatrists at		
ages $19-62^{\circ}$	$30^{a}$	,34 <sup>a</sup>
Inarticulate trait at age 19	$24^{a}$	.05
Use of repression at ages 19-47	21 <sup>b</sup>	12
Scholastic Aptitude Test (SAT)		
score at age 19	.06	07

<sup>&</sup>lt;sup>a</sup>p<.01. <sup>b</sup>p<.05.

which was quite unpredicted. Men at an autonomous or integrated ego level were four times as likely to have seen a psychiatrist 10 or more times as the men at the conscientious/conformist or conscientious level. Multiple regression analyses confirmed that this association was not an artifact: after partialing out the explained variance in psychiatrist visits contributed by measures of psychopathology and of alcoholism, the ego level still made an independent and significant contribution to the explained variance.

Table 3 attempts to explain why this paradoxical association of mature ego level with psychiatric visits should occur. Sentence Completion Test ego development level appeared to be associated with facets of psychiatric visits and with facets of ego maturity that seemed relatively independent of global mental health assessment. The correlations in table 3 reveal that mature ego level was significantly associated with psychological mindedness as reflected by articulateness, absence of repression, visits to psychiatrists, and intuition as a trait. Mature ego level was associated with creativity as reflected by frequent use of sublimation, inclusion in Who's Who in America, and a creative and intuitive trait. These correlations could not be explained by parental social class, intelligence, or income because ego development level and psychiatric visits were significantly correlated with none of these possibly confounding variables. On their Scholastic Aptitude Test (SAT) scores, men with low ego levels manifested greater mathematical than verbal attainment scores; however, verbal attainment scores per se did not distinguish men at different levels of ego development.

Unfortunately, our data do not make it possible to determine if high Sentence Completion Test ego level facilitated seeking help from psychiatrists or if psychotherapy facilitated ego development. To determine whether psychotherapy can increase one's ego level according to the Sentence Completion Test or whether the capacity to see ambiguities in life increases individuals' willingness to seek psychotherapy would require prospective studies and cross-lag analyses.

#### **DISCUSSION**

It is tempting to argue that adult adjustment at age 47 (i.e., "working and loving") should not be correlated with ego level measured by the Sentence Completion Test because the latter is just a "pencil and paper test" and in this way explain away our failure to find a significant correlation between the Sentence Completion Test findings and the clinically assessed maturity of defensive style. But such logic would miss the point that in general the Sentence Completion Test ego level does correlate with real life.

First, like the concept of defense mechanisms, Loevinger's concepts can be of great value to the clinician. Her explication of ego levels (7) and patients' illustrations of these levels through their completion of the Sentence Completion Test sentence stems helps us to appreciate discrepancies between the mind and affective language of the psychotherapist and those of the patient. This clinical appreciation of individual differences is comparable to Piaget's developmental stages, which help us to understand the discrepancies that occur between the logic and morality of the child and of the adult.

Second, review of empirical studies confirms that age predicts ego level according to the Sentence Completion Test (8, 23) as well as moral development (24) and maturity of defensive style (11). For boys between 9 and 18 years old, Loevinger and Wessler (1) reported that chronological age correlated with ego level with an r of .74. What is less certain is whether age is an important correlate of ego level after age 18. Studies by Loevinger et al. (25) suggested that freshmen students from competitive 4-year colleges manifested a distribution of ego level scores more similar to that of our sample at age 55 than to that of Holt's national probability sample drawn from all 2- and 4-year colleges regardless of quality (21).

Third, in our study, estimated psychosocial development was significantly correlated with *both* maturity of defensive style and Sentence Completion Test ego level. Fourth, Sullivan et al. (26) have provided evidence that the Sentence Completion Test and Kohlberg's scheme of moral development (10) correlate with a respectable r=.40, even with age partialled out. Finally, ego development as assessed by the Sentence Completion Test also correlated with assessments of ego identity in young adults (27). In addition, in an adolescent sample, mental health, Sentence Completion Test ego level, and maturity of defensive style were highly intercorrelated (28).

Thus, rather than dismissing the Sentence Completion Test as a "pencil and paper test," there are at least

cThe scoring system was reversed so that a low numerical score indicated "healthy" or "mature" for all measures. Thus, a low number of psychiatric visits received a low score.

four alternative explanations that may explain why in the present study ego level of maturity as measured by clinically assessed defenses failed to correlate significantly with ego level as measured by the Sentence Completion Test. First, as numerically assessed, maturity of defenses may be less a measure of ego maturation than an index of presence or absence of psychopathology. At present, the available data are inadequate to exclude this possibility (11, 12).

Second, ego development refers to the development of multiple processes, cognitive functions, defenses, and interpersonal skills. The Sentence Completion Test and maturity of defenses may measure independent processes. Work by Haan et al. (29) also found little correlation with maturity of defenses and Sentence Completion Test score in young adults.

Third, the developmental sequences reflected by shifts in Sentence Completion Test ego level and in ego defenses may reflect developmental lines that may have different alignments with age and education. Had our sample been assessed for Sentence Completion Test ego level and defensive maturity when in college, a greater correlation between the two variables might have been found.

Fourth, evidence has suggested that the Sentence Completion Test ego level depends inconsistently on intelligence (8), on education level (30), and on socio-economic status and father's level of education (23). High intelligence and educational attainment may be necessary, if not sufficient, requirements to achieve ego levels above conscientious (I-4) on the Sentence Completion Test.

We consider this final explanation the most likely. It is also consistent with a major criticism of the Sentence Completion Test: that verbal fluency powerfully correlates with a person's scored stage of ego level on the Sentence Completion Test. For example, the 32 men in our study who were placed at the conscientious/conformist level (I-3/4) or less used 88–342 words (mean=188) to complete their sentence stems. The 16 men who were placed at the individualistic level (I-5) or higher used 289–654 words (mean=432) to complete their stems. Only two of the 16 men at the individualistic level or higher used fewer than 300 words; only two of the 32 men at the conscientious/conformist level or less used more than 300 words.

This criticism, however true, does not invalidate the Sentence Completion Test as a measure of ego level. To control for verbosity per se, we contrasted 13 men at ego levels of individualistic and above with 26 men at the ego level of conscientious/conformist or conformist on two separate measures of spontaneous verbal behavior. First, we examined the word count on their written answers to questionnaire questions regarding their "philosophy over rough spots" and their views on disarmament. Although the men at higher ego levels tended to use more words than those at the lower level, the differences were entirely consistent with chance. We also examined their spoken answers by counting the number of words used to respond to

six Thematic Apperception Test (TAT) cards. The men with high ego levels used 321 to 1,774 words (mean=1,063), and the men with low ego levels used 489 to 2,299 words (mean=900)—again a completely insignificant difference. In short, number of words per response reflects both verbosity and an element of complexity of thought and psychological mindedness that is a legitimate index of ego level. For example, a man who was placed at a low ego level completed the sentence starting, "When I am with a woman," with "Wow!" and "My father and I" with "were close friends." In contrast, a man who was scored at the integrated level (I-6) completed "My father and I" with "never got really close. Mostly I remember confusion, embarrassment when he played the fool and hurt when he was furious with my mother."

Discussion of the dependence of the Sentence Completion Test on verbal fluency brings us to the fact that the test may serve as an indicator of psychological mindedness and creativity. If true, this would be extremely interesting. A limitation of any effort to measure creativity is that creativity is powerfully affected by intelligence and level of education. However, our sample had been preselected for relatively high intelligence, and 76% of our sample had pursued graduate education. In addition, as great a proportion of our sample as of Terman and Oden's sample of gifted subjects (31) were in Who's Who in America or in American Men and Women of Science. Thus, IQ and education per se were largely controlled in our sample.

The findings shown in table 3 suggest that the subjects who were viewed as cultural, ideational, creative, and intuitive in college were placed at a high ego level according to the Sentence Completion Test 30 years later. Such judgments in college were also supported by the fact that these individuals later scored high on sublimation and occupational distinction. That creativity may require more words is illustrated by contrasting the way a man placed at a mature ego level completed the sentence "When they avoided me." This man said, "I was delighted—I abhor the close attention of sharks." This contrasts with the pedestrian response of a man at the conformist level: "I took off." Or again, a trite and laconic man at the conformist stage completed "Rules are" with "made to be broken" in contrast to a man at the integrated level, who completed this sentence with "fences which make games possible and keep people from each other's throats." Rothenberg's Janusian theory of creativity (32) is also consistent with Loevinger's belief that the perception of ambiguity—"the ability to tolerate paradoxical relationships between events" reflects ego maturity. For example, one man with a high ego level completed the sentence "When he thought of his mother" with "he felt a mixture of pity and rage." Finally, the independence of Sentence Completion Test ego level from mental health but its close association with creativity and lack of repression (table 3) is also consistent with the work of McCrae and Costa (22),

who made observations very similar to ours.

In conclusion, for our sample, the Washington University Sentence Completion Test appears to be measuring something more limited than global ego maturity but far more interesting than simply age, intelligence, social class, and verbal fluency. The possibility that the Sentence Completion Test taps not just maturity of ego function but also psychological mindedness and creativity appears a real possibility and invites efforts at confirmation.

- Loevinger J, Wessler R: Measuring Ego Development, vol I: Construction and Use of a Sentence Completion Test. San Francisco, Jossey-Bass, 1970
- Vaillant GE: Theoretical hierarchy of adaptive ego mechanisms. Arch Gen Psychiatry 1971; 24:107–118
- Vaillant GE, Drake RE: Maturity of ego defenses in relation to DSM-III axis II personality disorder. Arch Gen Psychiatry 1985; 42:597-601
- Vaillant GE: Natural history of male psychological health, VII: effects of mental health on physical health. N Engl J Med 1979; 67:1249–1254
- Erikson E: Childhood and Society. New York, WW Norton, 1950
- Loevinger J: The meaning and measurement of ego development. Am Psychol 1966; 21:195–206
- Loevinger J: Ego Development. San Francisco, Jossey-Bass, 1976
- Hauser ST: Loevinger's model and measure of ego development: a critical review. Psychol Bull 1976; 83:928–955
- 9. Vaillant GE: Adaptation to Life. Boston, Little, Brown, 1977
- Kohlberg L: Development of moral character and moral ideology, in Review of Child Development Research, vol 1. Edited by Hoffman M, Hoffman L. New York, Russell Sage, 1964
- Vaillant GE: Natural history of male psychological health, V: the relation of choice of ego mechanisms of defense to adult adjustment. Arch Gen Psychiatry 1976; 33:535-545
   Vaillant GE, Bond M, Vaillant CO: An empirically validated
- Vaillant GE, Bond M, Vaillant CO: An empirically validated hierarchy of defense mechanisms. Arch Gen Psychiatry 1986; 43:786-794
- Heath CW: What People Are: A Study of Normal Young Men. Cambridge, Harvard University Press, 1945
- Vaillant GE (ed): Empirical Studies of Ego Mechanisms of Defense. Washington, DC, American Psychiatric Press, 1986

- Erikson E. Identity and the Life Cycle, Selected Papers. Psychol Issues 1959;
- Vaillant GE, Milofsky E: Natural history of male psychological health, IX: empirical evidence for Erikson's model of the life cycle. Am J Psychiatry 1980; 137:1348–1359
- 17. Luborsky L: Clinicians' judgments of mental health: a proposed scale. Arch Gen Psychiatry 1962; 7:407–417
- 18. Vaillant GE: Natural history of male psychological health, II: some antecedents of healthy adult adjustment. Arch Gen Psychiatry 1974; 31:15–22
- Vaillant GE: The Natural History of Alcoholism. Cambridge, Harvard University Press, 1983
- Hauser ST, Jacobson AM, Noam G, et al: Ego development and self-image complexity in early adolescence. Arch Gen Psychiatry 1983; 40:325–332
- Holt RR: Loevinger's measure of ego development: reliability and national norms for male and female short forms. J Pers Soc Psychol 1980; 39:909–920
- 22. McCrae RR, Costa PT: Openness to experience and ego level in Loevinger's Sentence Completion Test: dispositional contributions to developmental models of personality. J Pers Soc Psychol 1980; 39:1179–1190
- Loevinger J: Construct validity of the Sentence Completion Test of ego development. Applied Psychol Measurement 1979; 3: 281-311
- 24. Colby A, Kohlberg L, Gibbs J, et al: A Longitudinal Study of Moral Judgment. Monogr Soc Res Child Dev 1983; 48
- Loevinger J, Cohn LD, Bonneville LP, et al: Ego development in college. J Pers Soc Psychol 1985; 48:947–962
- Sullivan EV, McCullough G, Stager MA: A developmental study of the relationship between conceptual, ego and moral development. Child Dev 1970; 41:399–411
- 27. Adams GR, Shea JA: The relationship between identity status, locus of control and ego development. J Youth and Adolescence 1979; 8:81–89
- 28. Jacobson AM, Beardslee W, Hauser ST, et al: An approach to evaluating adolescent ego defense mechanisms using clinical interviews, in Empirical Studies of Ego Mechanisms of Defense. Edited by Vaillant GE. Washington, DC, American Psychiatric Press, 1986
- 29. Haan N, Stroud J, Holstein J: Moral and ego stages in relationship to ego processes: a study of "hippies." J Pers 1973; 41: 596-612
- 30. Snarey JR, Blasi JR: Ego development among adult kibbutzniks: a cross-cultural application of Loevinger's theory. Genet Psychol Monogr 1980; 102:117–157
- Terman LM, Oden MH: The Gifted Group at Midlife. Stanford, Calif, Stanford University Press, 1959
- 32. Rothenberg A: The process of Janusian thinking in creativity. Arch Gen Psychiatry 1971; 24:195–205

# New Technology in Convulsive Therapy: A Challenge in Training

The increase in seizure duration with caffeine sodium benzoate that is reported in two articles in this issue of the *Journal* is evidence of the growing complexity of convulsive therapy. We no longer expect to see a white-coated doctor—accompanied by brawny aides wheeling a treatment cart down the corridors of a large institution—moving from bed to bed, quickly inserting a mouth guard in an anxious patient and then applying some electrode jelly and electrodes to the temples, applying a stimulus and, after 1–2 minutes of the patient's seizure, quickly turning

the patient on his or her side and then moving on to the next bed.

Patients are now brought to well-equipped suites where a treatment team stands ready to check the patient's last meal and clinical condition, insert an intravenous line, inject atropine or glycopyrrolate, attach monitoring devices and electrodes for the treatment device, ventilate by mask with oxygen, inject a barbiturate and succinylcholine, and determine paralysis by muscle stimulator. A bite-block is inserted, the stimulus is applied, and a seizure with hardly a motor movement is monitored for duration. Ventilation and monitoring continue until the patient recovers. Monitoring devices are many: those for heart rate and rhythm, blood pressure, single-lead EEG, and cuff for seizure duration (1) are used routinely; in addition, an oximeter, muscle stimulator, and multilead EEG are used in sophisticated centers.

How did this change in practice come about? It is remarkable that use of a treatment which was introduced in 1934 has persisted. The principal impetus for its use has been the need to treat patients with psychoses that resist prevailing therapies. Queries from both the public and the profession about whether such an intrusive treatment serves a valid public purpose prompted numerous evaluations. Favorable reviews since 1976 by scientists and commissions in at least eight nations (2), culminating in the 1985 National Institutes of Health Consensus Conference Statement (3), reassured us that there was indeed a valid use for the treatment.

Doubts about the importance of the seizure in ECT led to studies, mainly in Great Britain, which showed that treatments with defined seizures were more effective than those with sham seizures (4). Studies of the differential effects of threshold and suprathreshold currents, brief-pulse and sinusoidal wave forms, and unilateral and bilateral electrode placements found differences in both the efficacy and the safety of these stimuli, allowing the knowledgeable clinician to arrange optimal treatments for different clinical conditions. For example, the EEG and cognitive changes following seizures are greater for sinusoidal than for brief-pulse currents and for bilateral than for unilateral electrode placements, suggesting that unilateral placements and brief-pulse currents are to be preferred for most treatments. Indeed, brief-pulse currents at threshold doses are associated with poorer clinical results than the same currents at suprathreshold doses, leading to the conclusion that threshold doses should not be used. The efficacy of treatments with bilateral placements is superior to that of treatments with unilateral placements, particularly among patients with severe affective disorders. Such placements are now used in treating patients with mania, severe inanition, and suicidal ideation (2, 5).

Seizures differ in pattern and duration. Seizures that appear to be "complete" and

similar in motor and EEG pattern may differ in efficacy, leading to questions about the characteristics of a clinically effective seizure. At this juncture we are not sure, although a full or complete motor and EEG seizure seems better than an incomplete or short seizure. How are we to define a full seizure? The best clinical measure remains seizure duration, hence the interest in monitoring seizure durations by the cuff, the EEG, or the heart rate method (1). A single-lead EEG has been a feature of two of the recently developed brief-pulse ECT devices, the Thymatron and the MECTA SR-1.

We are not secure in defining the duration of an adequate seizure. Seizure durations shown on the EEG and heart rate monitors are longer by 10%–20% than seizure durations measured by motor activity (1, 5). In conventional thinking, motor seizure durations of less than 25 or 30 seconds, as measured by cuff monitoring, are considered to be short or missed, durations longer than 120 seconds to be prolonged, and durations between 25 and 120 seconds to be optimal.

A prolonged seizure, which is usually seen on the EEG and heart rate monitors, is readily aborted by intravenous barbiturate or diazepam. For a brief seizure, the usual practice is to repeat the stimulus under the same anesthesia, using a greater stimulus energy. But what if, despite the delivery of maximum currents from the ECT device, the patient still has a partial seizure? Such an event is likely if the therapist uses induction currents near the seizure threshold, particularly since seizure thresholds generally rise during the course of therapy and are high in the elderly, especially men (2, 5).

One expedient is to use the maximum energy delivered by the treatment device for all patients. While the use of maximum doses is a feature of much present practice, it carries the risk, particularly in younger adults, of prolonged seizures, greater cognitive impairment, and enhanced EEG abnormality during the treatment course.

With sinusoidal current devices, which deliver high energies, the incidence of missed seizures is low and can be further circumvented by double stimulation. Brief-pulse devices reemerged in the 1970s in response to anxieties about the cognitive impairment associated with the use of ECT. When they were introduced, their maximum energy output was intentionally restricted, leading to an increased incidence of missed and incomplete seizures (5).

Missed seizures then became a problem. Since benzodiazepines and barbiturates given as nighttime sedatives raise seizure thresholds and decrease treatment efficacy, their routine use was discouraged. Alternative anesthetics were examined, and etomidate was found to be an anesthetic without seizure threshold enhancement (6). Newer treatment devices with greater output intensities have been introduced in the United States in the past 3 years (e.g., Somatics' Thymatron, MECTA SR-1, Medcraft B-25, and ElCoT MF-1000).

The increase in seizure duration by pretreatment with caffeine sodium benzoate reported by Shapira et al. (7) provided another answer. The reports in this issue of the *Journal* support this observation. In patients with high seizure thresholds, pretreatment with intravenous caffeine sodium benzoate in doses of 0.5–1.0 g, 5–10 minutes before induction, will increase seizure duration, often to a clinically acceptable degree. While the study by Shapira et al. limited the patient sample to those without cardiovascular disease, the study by Hinkle and associates included high-risk patients with medical disabilities, which suggests that the administration of caffeine sodium benzoate is safe even in the face of such disability.

Both groups used the MECTA C for their cases. Hinkle et al. used the higher-energy Thymatron for one patient, showing that even when patients are treated with higher-energy instruments, elevated seizure thresholds may still be a problem.

There are practical difficulties in implementing pretreatment with caffeine. Caffeine sodium benzoate is almost impossible to obtain in the United States, since the Food and Drug Administration (FDA) has characterized the compound as "ineffective" for other uses. Pentylenetetrazole (Metrazol) was the compound used in earlier decades to enhance seizure efficacy (2). A similar determination of its effectiveness by the FDA led to its withdrawal from the market, not only in the United States but in all markets except Hungary. The report of a prolonged seizure and death in a patient who received theophylline, a compound chemically related to caffeine, suggests that

safety studies are required. In addition, parametric studies to define the optimal dose and time for caffeine administration are yet to be done.

Rather than embarking on these experimental routes, what can a prudent electrotherapist do when seizure duration is compromised? The first step is to eliminate the routine use of benzodiazepines or barbiturates for sedation. A change to a higher-energy ECT device, the induction of hyperventilation and hyperoxygenation before inducing a seizure, and a change of electrode placement to the unilateral position (seizure thresholds are lower with this placement) should be considered next. The dose of anesthetic may be lowered, or a change to etomidate can be made. Double stimulation is also possible, although there are concerns that high electrical energies may be associated with greater cognitive effects. If these maneuvers fail, the administration of caffeine sodium benzoate as outlined by the authors of these *Journal* articles may be effective.

The reports of Shapira et al. and Hinkle et al. illustrate changes in ECT practice that have made modern convulsive therapy a complex technology. After deciding on the use of ECT for patients with various mental disorders, therapists must now choose among a variety of currents and electrode placements for induction; decide whether to continue or discontinue psychoactive drug treatment; select an appropriate anesthetic; determine the adequacy of each seizure by monitoring duration and seizure pattern; and manage the physiologic changes in cardiac, pulmonary, and central nervous systems that accompany the treatments. The latter is particularly important in high-risk medically ill and elderly patients, for whom ECT is often a reliable option. To these technical changes must also be added the special demands for informed consent by patients and their families, especially in those institutions and states where special rules for ECT apply.

It may no longer be sufficient for psychiatrists to assert their skill in ECT on the basis of the lecture experience provided in conventional training programs. Many educational programs at medical school and residency levels are clearly deficient (8). Board certification in psychiatry requires no evidence of experience or practical knowledge of convulsive therapy or of its physiologic accompaniments; thus, it may be unwise to automatically give certified psychiatrists privileges in ECT (9). In 1975 the American Psychiatric Association responded to the criticism of ECT use by establishing the Task Force on Electroconvulsive Therapy. The task force report (10) reassured the profession and the public about the proper use of ECT and encouraged the increase in research interest and clinical use. With the growing complexity of ECT practice, however, it is time for the Association to examine training practices in medical schools, psychiatric residency, and continuing medical education programs and the criteria for certification in psychiatry. As the editors of Lancet noted, in response to the assessment of British ECT practice reported in the historic survey by Pippard and Ellam (11) "If ECT is ever legislated against or falls into disuse it will not be because it is an ineffective or dangerous treatment; it will be because psychiatrists have failed to supervise or monitor its use adequately" (12).

- Fink M, Johnson L: Monitoring duration of ECT seizures: "cuff" and EEG methods compared. Arch Gen Psychiatry 1982; 39:1189–1191
- 2. Fink M: Convulsive Therapy. New York, Raven Press, 1979
- 3. Consensus conference: electroconvulsive therapy. JAMA 1985; 254:2103-2108
- 4. Palmer RL (ed): Electroconvulsive Therapy: An Appraisal. New York, Oxford University Press, 1981
- Malitz S, Sackeim H (eds): Electroconvulsive Therapy: Clinical and Basic Research Issues. Ann NY Acad Sci 1986; 462
- Christensen P, Kragh-Sørenson P, Sørenson C, et al: EEG-monitored ECT: a comparison of seizure duration under anesthesia with etomidate and thiopentone. Convulsive Therapy 1986; 2:145–150
- Shapira B, Zohar J, Newman M, et al: Potentiation of seizure length and clinical response to electroconvulsive therapy by caffeine pretreatment: a case report. Convulsive Therapy 1985; 1:58– 60
- Raskin DE: A survey of electroconvulsive therapy: use and training in university hospitals in 1984.
   Convulsive Therapy 1986; 2:293–296
- 9. Fink M: Training in convulsive therapy. Convulsive Therapy 1986; 2:227-230

- American Psychiatric Association Task Force Report 14: Electroconvulsive Therapy. Washington, DC, APA 1978
- 11. Pippard J, Ellam L: ECT in Great Britain, 1980. Gaskell, London, 1981
- 12. EĈT in Britain: a shameful state of affairs (editorial). Lancet 1981; 2:1207-1208

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# Foundations' Fund Prize for Research in Psychiatry

The American Psychiatric Association takes pleasure in inviting submissions for the eleventh annual Foundations' Fund Prize for Research in Psychiatry.

Candidates for this prize should be citizens of the United States or Canada and should be nominated by a sponsor. Sponsors should be members of the American Psychiatric Association. Members of the prize board are excluded from submitting nominations.

The *sponsor* should submit a supporting letter (six copies) setting out in detail justification for the nomination and summarizing the research accomplishments of the nominee in a specific area or with a coherent theme.

The nominee should submit

- 1) A book or paper (six copies) or a group of representative and thematically linked books or papers (six copies) published in English (or accepted for publication) and dated within 10 years prior to the deadline of submission;
- 2) A summary statement (six copies) written by the nominee, emphasizing the principal theme running through the work, its internal cohesiveness and consistency, and scientific implications;
- 3) An up-to-date curriculum vitae (six copies);
- 4) An up-to-date bibliography (six copies).

All entries must be submitted in six complete collated sets and sent to Ira D. Glick, M.D., Chairman, Foundations' Fund Prize Board for Research in Psychiatry, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Entries will be acknowledged but cannot be returned. The prize is based on a yearly competition and resubmission is permitted. The award will be presented at the Convocation of Fellows at the Association's annual meeting in May 1988.

The deadline for submission is November 1, 1987.

# Facilitation of ECT by Caffeine Pretreatment

Baruch Shapira, M.D., Bernard Lerer, M.D., Dror Gilboa, B.A., Heinz Drexler, M.D., Sol Kugelmass, Ph.D., and Avraham Calev, D.Phil.

In this study, eight patients participated in a standardized protocol to assess the effects of caffeine on seizures in ECT. Caffeine sodium benzoate (500–2000 mg) was administered intravenously 10 minutes before ECT, and seizure duration was compared with that of a previous treatment unmodified by caffeine. Seizure duration was significantly increased during ECTs preceded by caffeine. Three other patients given caffeine when seizures of adequate duration could no longer be elicited at maximal stimulus levels experienced longer seizures. Administration of caffeine was not associated with significant cardiovascular or other (including cognitive) adverse effects.

(Am J Psychiatry 1987; 144:1199-1202)

Clinicians have long been aware that over the course of an ECT series, increasing levels of electrical stimulation are often needed to elicit a generalized seizure. The concomitant reduction in seizure duration may impair the therapeutic efficacy of the treatment (1). Adverse cognitive effects of ECT may be exacerbated because of the adjustments in current intensity and stimulus waveform that are used to ensure the elicitation of a seizure. Interventions that can be safely used to enhance seizure duration are therefore of considerable clinical importance. Pre-ECT administration of pentylenetetrazole in subconvulsive doses has been shown to increase the length of seizures (2), but this agent is no longer commercially available.

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Shapira et al. (3) reported that pretreatment administration of caffeine sodium benzoate (250–1000 mg i.v.) increased seizure length and improved therapeutic outcome in a severely depressed patient. The purpose of the present project was to study the effect of caffeine pretreatment on seizure induction during ECT under standardized conditions and to evaluate the safety of this intervention.

# **METHOD**

Patients considered clinically eligible for ECT because of major depression (by DSM-III criteria) were asked to participate in the study. Informed consent was obtained in accordance with Jerusalem Mental Health Center institutional review board procedures. Patients with cardiovascular disease or any other major physical illness were excluded. Six female and two male patients entered the standardized study protocol. Their mean±SD age was 55.6±9.12 years, and their mean±SD pretreatment Hamilton Rating Scale for Depression score was 29.8±6.36; four patients had a unipolar disorder and four a bipolar disorder. In addition, three other depressed patients (a 64-year-old man and two women, 60 and 71 years old) who had not been initially included in the study were given caffeine during their ECT course when maximal settings on the MECTA apparatus failed to elicit clinically adequate seizures.

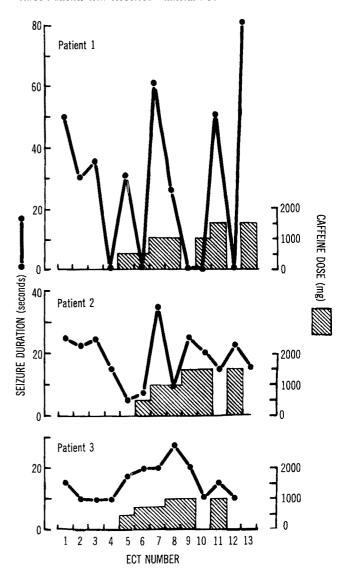
Treatments were administered three times a week by means of a MECTA Model D apparatus with bitemporal electrode placement. Anesthesia was induced by sodium pentothal (3.0 mg/kg) and succinylcholine (1.5 mg/kg) followed by oxygenation. Seizure duration was monitored centrally by the MECTA single-channel EEG monitor and peripherally in a lower limb by occlusion of the systolic blood supply before the administration of succinylcholine. Because of contro-

versy about the precise delineation of the end point of EEG-monitored seizures (4), peripheral seizure length was the operational criterion we used. Seizure threshold was defined as that current intensity (in milliampere-seconds) which elicited a generalized seizure that lasted more than 20 seconds. Threshold was established by a method-of-limits technique first described by Malitz et al. (5). During the first treatment, initial MECTA settings were a 30-Hz frequency, a 1.5-msec pulse width, and a 1.0-second pulse train duration (72) mA-seconds). If a seizure exceeding 20 seconds in length was not induced, the patient was restimulated no less than 40 seconds later at a 50-Hz frequency (120 mA-seconds) and, if needed (no less than 40 seconds later), at 70 Hz (168 mA-seconds). In order to further increase stimulus intensity, pulse train duration could be raised to 1.5 seconds (252 mA-seconds) and then to 2.0 seconds (336 mA-seconds). However, no more than three stimulations were attempted in a single treatment session. During subsequent treatments, seizure threshold was determined by a modification of the procedure we have described, which was designed to eliminate unnecessary stimulations. For treatments not preceded by the administration of caffeine, the initial setting was one below the level that had previously induced a seizure; for treatments preceded by caffeine, the setting was two below the previous threshold.

The procedure for administering caffeine to the eight patients participating in the standardized protocol was as follows. Caffeine sodium benzoate was administered before one of treatments 2-4, 6-8, and 10-12. Seizure threshold had been determined during the previous treatment and was again determined in conjunction with administration of caffeine. Peripheral seizure length was noted for both treatments. The caffeine was given intravenously 10 minutes before the anesthetic was administered, at a starting dose of 500– 1000 mg, while the patient was at rest in the treatment room. (The increase in initial dose was decided upon during the protocol when effects on seizure threshold and duration were not observed at the lower doses.) Clinical responses were closely observed, and pulse and blood pressure measurements, taken at baseline, were repeated before the anesthetic was administered and immediately after completion of the seizure. The dose of caffeine was increased by 250-500 mg during subsequent administrations if adverse effects had not been observed and no effects or minimal effects on seizure threshold and duration had been documented. Details of caffeine administration in the three patients treated outside the standardized protocol are shown in figure 1.

Six of the eight patients who participated in the standardized protocol were administered a battery of cognitive tests in conjunction with ECT (with and without caffeine pretreatment) during each of the three treatment phases. The test battery was derived from that previously described by Sackeim et al. (6) and encompassed 1) orientation time to a criterion of 75%

FIGURE 1. Effect of Caffeine Pretreatment on Seizure Duration in Three Patients Who Received Bilateral ECT



relative to baseline, 2) word fluency by letter and category, tested 1 hour after ECT, followed by 3) retrograde memory for words and designs (recall and recognition) and faces (recognition) learned 5–15 minutes before ECT, and 4) anterograde memory for words and designs (recall and recognition) learned 1½ hours after ECT and tested immediately and 20 minutes later.

Seizure threshold and seizure duration after administration of caffeine were compared to the corresponding measurements for the immediately preceding treatment, which was unmodified by caffeine, by a paired t test (two-tailed). Cognitive performance with and without caffeine pretreatment was compared by paired t tests (two-tailed) or by analysis of variance with repeated measures. Correlations were performed by means of Pearson coefficients. Results are shown as mean±SD or as median and range.

TABLE 1. Effect of Caffeine Pretreatment on Seizure Threshold and Seizure Duration During ECT in Eight Depressed Patients

	Caffeine	Dose (mg)	Seizure Threshol	d (mA-seconds)	Seizure Duration (seconds)		
Condition	Median	Range	Mean	SD	Mean	SD	
ECTs 1-4							
No caffeine			157	48.2	50	11.4	
Caffeine	500	500-1000	169	77.2	56	13.4	
ECTs 5-8							
No caffeine			168	52.8	36	12.4	
Caffeine	1000	500-1250	199	71.4	61 <sup>a</sup>	28.1	
ECTs 9-12b				;			
No caffeine			224	83.6	31	6.2	
Caffeine	1500	500-2000	233	98.0	45°	7.9	

<sup>&</sup>lt;sup>a</sup>Significant difference between caffeine and no-caffeine ECTs (t=2.71, df=7, p<.05, paired two-tailed test).

# **RESULTS**

All eight patients in the standardized protocol received 12 ECT administrations over a period of 4 weeks. The effects of caffeine pretreatment on seizure threshold and seizure duration during the three treatment phases (ECTs 1-4, 5-8, and 9-12) are shown in table 1. For technical reasons, seizure measurements were not obtained for one patient during the third treatment phase; the number of subjects for this phase was therefore seven. Unmodified by caffeine, seizure threshold increased by 30% from the first treatment to the final treatment. Seizure threshold was not significantly altered by caffeine administration at any stage. Seizure duration (unmodified by caffeine) declined 39% from the first treatment to the last. Caffeine administration significantly increased seizure length during treatments 6-8 and 9-12 (comparison in each case is with the immediately preceding treatment, which was unmodified by caffeine).

Figure 1 shows the treatment course in the three patients who received caffeine in the clinical context. The reduction in seizure duration (at maximal stimulation with 336 mA-seconds) that necessitated caffeine administration is evident in all three cases. Seizure duration increased when caffeine pretreatment was instituted (without change in threshold) but again declined in all cases as the treatment progressed, in spite of the previously effective caffeine dose. Increased caffeine dosage was needed in order to maintain a therapeutically adequate seizure duration.

Across all trials the mean pulse rate was  $83.9\pm17.40$  beats per minute before administration of caffeine,  $91.7\pm18.40$  beats per minute 10 minutes after caffeine, and  $91.9\pm18.8$  beats per minute after completion of the seizure ( $86.6\pm16.30$  beats per minute without caffeine). The mean systolic blood pressure was  $148\pm33.7$  mm Hg before caffeine,  $170\pm27.9$  mm Hg 10 minutes after caffeine, and  $196\pm44.00$  mm Hg after completion of the seizure ( $182\pm35.50$  mm Hg without caffeine). The mean diastolic blood pressure was  $86\pm15.00$  mm Hg before caffeine,  $90\pm10.9$  mm Hg 10 minutes after caffeine, and  $102\pm18.00$  mm Hg after seizure ( $97\pm14.60$  mm Hg without caffeine).

TABLE 2. Effect of Caffeine Pretreatment on Orientation Time After ECT in Eight Depressed Patients

Condition	Orientation Time After ECT (minutes)					
	Mean	SD				
ECTs 1-4						
No caffeine	50.00	22.58				
Caffeine	45.00	25.09				
ECTs 5-8						
No caffeine	32.50	6.12				
Caffeine	40.00	20.49				
ECTs 9-12						
No caffeine	27.50	6.12				
Caffeine	37.50	15.73				

None of the caffeine effects on pulse or blood pressure were statistically significant.

As shown in table 2, orientation time diminished over the ECT series in treatments unmodified by caffeine. This reduction was less prominent in the case of treatments preceded by caffeine, but not to a statistically significant extent. Of the remaining 15 cognitive variables compared during each of the three treatment phases (45 comparisons in all), only two (both were design recognition variables) showed worsening after caffeine pretreatment. Pearson correlations of caffeine dose, stimulus intensity, and seizure duration with orientation time as well as with each of the cognitive measures were calculated. No consistent effect of caffeine dose or stimulus intensity emerged. Increased seizure duration was significantly related to impaired performance on six of 48 correlations during the three treatment phases (p<.05). However, two correlations showed impaired performance associated with reduced seizure duration (p<.05).

No serious untoward effects of caffeine were observed clinically. On three occasions, patients who had received caffeine were observed to be restless in the initial postictal period but required no specific treatment. One patient was observed to be agitated, and another manifested a fine tremor during the 10 minutes between administration of caffeine and induction of anesthesia. Subjective feelings of restlessness were

bN=7; data for one patient in this phase are not available.

Significant difference between caffeine and no-caffeine ECTs (t=4.00, df=6, p<.01, paired two-tailed test).

more frequent at higher caffeine doses but were well tolerated.

# **DISCUSSION**

The present findings confirm and extend our previous clinical report (3) of increased seizure duration after pretreatment with caffeine. It is interesting, in view of the preclinical effects of methylxanthine administration (7, 8), that caffeine administration did not reduce seizure threshold at any stage. This negative finding may, however, have been a function of the method-of-limits technique used for determining seizure threshold, which involves large increments in stimulus intensity. Smaller reductions in threshold could well be missed when the procedure is used. The fact that seizure duration was significantly increased by caffeine in treatment 6 and thereafter, but not before this stage, is of interest. It could be related to the lower dose of caffeine used in the earlier treatments (table 1). However, two of the patients who were given caffeine when they became resistant to adequate seizure induction at maximal stimulation responded to initial caffeine doses of 500 mg, which raises the possibility that enhancement of seizure duration by the administration of caffeine may be more effective at higher threshold levels. This is, however, the context in which caffeine pretreatment would be most applicable clinically.

Administration of caffeine before ECT was not found to be associated with a greater frequency of clinically significant adverse effects. Subjectively, the treatment was well tolerated even at the higher doses. Effects on pulse and blood pressure levels were modest and did not suggest a negative interactive effect of caffeine and ECT on these variables. Scores on the cognitive test battery showed only minor adverse effects of caffeine on orientation time and cognitive performance. These may have been related to the increase in seizure duration induced by caffeine. Miller et al. (9) reported a positive correlation between seizure duration and forgetting of nonverbal material in patients given unilateral ECT. It therefore seems prudent to avoid doses of caffeine that result in excessive increases in seizure duration. This is particularly important in view of a report of status epilepticus as a consequence of ECT in an asthmatic patient with plasma levels of the methylxanthine, theophylline, above the accepted therapeutic range but below the level generally associated with seizures (10).

We (3) previously suggested that the effect of caffeine in increasing seizure duration may be related to its adenosine antagonist properties. Newman et al. (11) reported that a series of chronic electroconvulsive shocks given to rats led to an increase in adenosine  $A_1$  receptor binding. This receptor has been linked to an anticonvulsant action (12). Caffeine has been shown to have an inhibitory effect on  $A_1$  adenosine receptors (7) and to increase seizure duration in animals (8). If this proposed mechanism indeed underlies the clinical action of caffeine on the duration of seizures, a similar effect should be observed after administration of other methylxanthines that inhibit adenosine  $A_1$  receptors.

The present findings suggest a role for caffeine sodium benzoate as a safe and effective adjunct to ECT. Pretreatment with caffeine is recommended for patients undergoing ECT who are physically healthy and in whom seizures of adequate therapeutic length cannot be elicited by conventional techniques. Further studies are needed to define optimum dosage more accurately and to establish the limits of safety in elderly patients and those with impaired cardiovascular function.

- Fink M: Convulsive Therapy: Theory and Practice. New York, Raven Press, 1979
- Holmberg G, Haard G, Ramqvist N: Experiments in the prolongation of convulsions induced by electric shock treatment. Acta Psychiatr Neurol Scand 1956; 31:61-70
- Shapira B, Zohar J, Newman M, et al: Potentiation of seizure length and clinical response to ECT by caffeine pretreatment. Convulsive Therapy 1985; 1:58-60
- Ries RK: Poor interrater reliability of MECTA EEG seizure duration measurement during ECT. Biol Psychiatry 1985; 20: 94-98
- Malitz S, Sackeim HA, Decina P: ECT in the treatment of major affective disorders: clinical and basic research issues. Psychiatr J Univ Ottawa 1982; 7:126–134
- Sackeim HA, Portnoy S, Neeley P, et al: Cognitive consequences
  of low-dosage electroconvulsive therapy, in Electroconvulsive
  Therapy: Clinical and Basic Research Issues. Edited by Malitz S,
  Sackeim HA. New York, New York Academy of Sciences, 1986
- Daly JW, Bruns RF, Snyder SH: Adenosine receptors in the central nervous system: relationship to the central actions of methylxanthines. Life Sci 1981; 28:2083–2097
- Albertson TE, Joy RM, Stark LG: Caffeine modification of kindled amygdaloid seizures. Pharmacol Biochem Behav 1983; 19:339–343
- Miller AL, Faber RA, Hatch JP, et al: Factors affecting amnesia, seizure duration, and efficacy in ECT. Am J Psychiatry 1985; 142:692-696
- Peters SG: Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. Mayo Clin Proc 1984; 59:568–570
- 11. Newman M, Zohar J, Kalian M, et al: The effects of chronic lithium and ECT on A<sub>1</sub> and A<sub>2</sub> adenosine receptor systems in rat brain. Brain Res 1984; 291:188–192
- Dunwiddie TV, Worth T: Sedative and anticonvulsant effects of adenosine analogs in mouse and rat. J Pharmacol Exp Ther 1982; 220:70-76

# Prevalence of Specific Suicidal Behaviors in a High School Sample

Jill M. Harkavy Friedman, Ph.D., Gregory M. Asnis, M.D., Marjorie Boeck, Ph.D., M.D., and Justine DiFiore

Of 380 high school students who completed an anonymous survey concerned with their experience with suicidal behavior, 60% reported that they had thought about killing themselves. These thoughts varied with respect to persistence and planfulness. Almost 9% reported that they had actually made at least one attempt to kill themselves and over half of the suicide attempters reported at least two attempts. Fewer than half of the attempters reached the attention of mental health professionals. The data on family history of suicidal behavior suggest that the suicidal ideators and the suicide attempters represent overlapping groups.

(Am J Psychiatry 1987; 144:1203-1206)

A lmost one-quarter of all adolescent deaths are from suicide. The frequency and form of other suicidal or self-destructive behaviors (i.e., thoughts, plans, and attempts) in this age group remain relatively unclear. If the range of suicidal behaviors reflects an underlying continuum or spectrum rather than discrete behaviors, information regarding each type of suicidal behavior is important. Without such information, the development of effective intervention and prevention techniques is difficult.

The prevalence of suicidal behavior in the general population and among specific subgroups has been minimally studied. The prevalence of suicidal ideation among adults has been explored primarily via epidemiological studies (1–4). According to these investigations, 2.3%–55% of those interviewed or surveyed reported that they had engaged in some type of suicidal ideation, and 0.6%–2.7% reported that they had

made at least one suicide attempt. The only one of these studies that used an anonymous survey (4) rather than extensive interviews reported the highest rates. High rates were also reported when the time frame asked about reflected a lifetime prevalence rate rather than a point prevalence rate.

Investigating the prevalence of suicidal behavior among children and adolescents, Pfeffer et al. indicated that 9% of the 6- to 15-year-old school children interviewed reported some type of suicidal ideation (5), that 1% reported they had made at least one suicide attempt (5), and that 33% of those identified as psychiatric outpatients reported engaging in some type of suicidal behavior (6). The prevalence of suicidal behavior among child and adolescent psychiatric inpatients has been reported to range between 65% and 78.5% (5, 7–9). According to all of these prevalence rates, child and adolescent psychiatric inpatients engage in more suicidal behavior than psychiatric outpatients of the same age group, children and adolescents engage in more suicidal behavior than adults in the general population, and those responding to anonymous surveys report more suicidal behavior than those being interviewed.

Generalizations from these studies to the general high school adolescent population would be premature. First, none of the prevalence studies included assessments of high school students, and many involved the study of young psychiatric patients. Therefore, the attempters studied may represent a restricted subsample of all suicide attempters—those who were seen in psychiatric or other medical facilities. Second, the use of interview techniques to assess the prevalence of suicidal behavior requires a thorough, interactive procedure. Interview techniques are labor intensive and require good rapport between the interviewer and the interviewee; it is unclear how the face-to-face nature of interviewing affects the reporting of suicidal and self-destructive behavior, particularly among adolescents. Some research has suggested that anonymous surveys provide greater information regarding prevalence rates (10, 11) and that the reliability and validity of anonymous surveys can be tested and established

We present the preliminary results from the responses of 380 students to an anonymous survey

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TABLE 1. Demographic Characteristics of 380 High School Students Who Responded to a Survey on Suicidal Behavior

	Total S (N=3			No Suicidal Behavior (N=146)		Suicidal Ideators (N=201) <sup>a</sup>		Suicide Attempters (N=33)	
Variable	N	%	N	%	N	%	N	%	
Sex <sup>b</sup>									
Male	200	53	90	62	102	51	8	24	
Female	180	47	56	38	99	49	25	76	
Grade									
9	87	23	39	27	43	21	5	15	
10	91	24	29	20	52	26	10	30	
11	86	23	35	24 29	41	21	10	30	
12	115	30	43	29	64	32	8	24	
Race									
White	190	50	71	49	103	51	16	49	
Black	50	13	20	14	23	11	7	21	
Hispanic	37	10	13	9	19	10	5	15	
Oriental	81	21	30	20	47	23	4	12	
Other	22	6	12	8	9	5	1	3	
Religion									
Catholic	117	31	46	32	56	28	15	46	
Protestant	60	16	19	13	36	18	5	15	
Jewish	71	19	28	19	36	18	7	21	
Other	60	16	22	15	33	16	5	15	
None	71	19	31	21	39	20	1	3	
Experience with counseling <sup>c</sup>	73	19	10	7	42	21	21	64	

<sup>&</sup>lt;sup>a</sup>Only 200 of the 201 ideators answered the questions about grade and religion.

TABLE 2. Experience With Suicidal Behavior Among Family and Associates Reported by 380 High School Students Who Responded to a Survey on Suicidal Behavior

			S	tudent Grouj	9			
No Suicidal Behavior (N=146)			Suicidal Ideators (N=201)			Suicide Attempters (N=33)		
Acquainted With Suicidal Person		Acquainted With Suicidal Person					Acquainted With Suicidal Person	
Total	Ŋ	%	Total	N	%	Total	N	%
142 145	16 55	11.3 37.9 41.1	187 196 201	54 97	28.9 49.5 55.7	31 33 33	9 22 26	29.0 66.7 78.8
	Total 142 145	Behavior (N=1)   Acquain   Suicide     Total   N     142   16	Behavior (N=146)           Acquainted With Suicidal Person           Total         N         %           142         16         11.3           145         55         37.9	No Suicidal Behavior (N=146)         Ide           Acquainted With Suicidal Person           Total         N         %         Total           142         16         11.3         187           145         55         37.9         196	No Suicidal Behavior (N=146)         Suicidal Ideators (N=20)           Acquainted With Suicidal Person         Acquainted Suicidal Person           Total         N         %         Total         N           142         16         11.3         187         54           145         55         37.9         196         97	Behavior (N=146)         Ideators (N=201)           Acquainted With Suicidal Person         Acquainted With Suicidal Person           Total         N         %           142         16         11.3         187         54         28.9           145         55         37.9         196         97         49.5	No Suicidal Behavior (N=146)         Suicidal Ideators (N=201)         Atternal Acquainted With Suicidal Person         Acquainted With Suicidal Person         Acquainted With Suicidal Person         Total N %         Total N %	No Suicidal Behavior (N=146)         Suicidal Ideators (N=201)         Suicide Attempters (N=201)           Acquainted With Suicidal Person         Acquainted With Suicidal Person         Suicidal Person         Suicidal Person           Total         N         %         Total         N         %         Total         N           142         16         11.3         187         54         28.9         31         9           145         55         37.9         196         97         49.5         33         22

<sup>&</sup>lt;sup>a</sup>Significant difference between groups ( $\chi^2$ =15.61, df=2, p<.001). <sup>b</sup>Significant difference between groups ( $\chi^2$ =10.38, df=2, p>.006).

concerned with their experience with suicidal behaviors, focusing on the prevalence of specific forms of suicidal behavior.

# **METHOD**

Of 385 students attending an academically select public high school in New York who were asked to complete an anonymous survey packet, 382 actually completed the packet; two of these were not included in our study sample because relevant data were missing. The mean ±SD age of the total sample (N=380) was 16.04±1.2 years; other demographic characteristics of the 380 students are presented in table 1. We used a stratified random sampling technique to select the sample. For each grade level, three social studies

classes (a required subject) were randomly selected from each grade and invited to participate in the study. The study sample of 200 males and 180 females was demographically consistent with the entire school population. There were approximately equal numbers of students from each of the four grades, and the sample was heterogeneous with respect to race and religion.

As part of a comprehensive survey packet, the students were asked to complete the Harkavy Asnis suicide survey demographic form, a questionnaire that ascertains basic demographic data (i.e., age, grade, race, religion), data on past psychiatric or counseling history, and specifics about their experience with their own suicidal behavior and that of their family and peers (tables 1 and 2).

All surveys were completed during one 40-minute class period. At the beginning of the period, one of the

bSignificant difference between groups ( $\chi^2=15.71$ , df=2, p<.0001). Significant difference between groups ( $\chi^2=56.25$ , df=2, p<.001).

investigators (J.M.H.F.) introduced the purpose of the study. The students were provided with a list of mental health resources within and outside of the school that were available to them and were encouraged to seek help at these facilities if needed. The survey packet was administered after students were reminded of their right to refuse to participate. Anonymity was maintained for all participants.

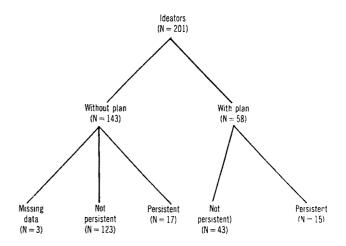
Chi-square tests were used to test for significant group differences (no suicidal behavior, suicidal ideators, and suicide attempters) when groups were compared on categorical variables (i.e., demographic variables and family history). Analysis of variance (ANOVA) was used to compare groups on continuous variables such as age.

# RESULTS

Of the 380 high school students, 146 (38.4%) stated that they had never thought about killing themselves (no suicidal behavior group), 201 (52.9%) stated that they had "thought about killing themselves but did not actually try" (suicidal ideator group), and 33 (8.7%) stated that they had tried to kill themselves at least once (suicide attempter group) (table 1). There were no significant differences among the three groups with respect to distribution of grade, race, or religion. There was no significant main effect for age (mean ±SD age=15.97±1.2 years for the no suicidal behavior group; 16.07±1.2 years for the ideators; and 16.15± 1.2 years for the attempters). The three groups differed significantly with respect to sex distribution: the no suicidal behavior group consisted of more boys than girls, the suicidal ideators had equal numbers of boys and girls, and the reported suicide attempters had significantly more girls than boys. The groups also differed significantly with respect to their past involvement in some type of counseling: suicide attempters reported more experience with counseling than did ideators, who reported more experience with counseling than did those reporting no suicidal behavior.

The three groups were compared with respect to their experience with other individuals who had engaged in suicidal behavior (table 2). There was a significant group effect with respect to experience with suicidal behavior among family members: the ideators and attempters reported more suicidal behavior among family members than did those in the no suicidal behavior group, but ideators did not differ significantly from attempters with respect to experience with suicidal behavior among family members. The three groups also differed significantly with respect to experience with suicidal behavior among their peers or associates: more ideators reported knowing about suicidal behavior among their associates than did those in the no suicidal behavior group, and more attempters than ideators reported knowing at least one peer or associate who had engaged in suicidal behavior at some time.

FIGURE 1. Persistence and Planfulness of Suicidal Ideas Among High School Suicidal Ideators



To better describe the ideation of the 201 students who reported that they had "thought about killing themselves but did not actually try," their data were further categorized with respect to persistence and planfulness (see figure 1). If students reported thoughts that "persisted for at least 7 days in a row," their thoughts were described as persistent. If students responded "yes" to "Did you have a plan?" and could describe a plan of any type, their thoughts were considered planful. Of the 201 ideators, 166 reported that their thoughts were not persistent, and 123 reported that their ideas were not persistent and did not involve a plan. Seventeen students reported persistent ideas without a plan, and 43 students reported that they had a plan but their thoughts were not persistent. There was a significant effect for sex ( $\chi^2 = 14.25$ , df=3, p<.003): more boys than expected reported no suicidal thoughts, and more girls than expected reported planful and persistent thoughts. There was also a significant effect for race ( $\chi^2$ =33.66, df=12, p<.001): more whites than expected reported no suicidal thoughts and more Orientals than expected reported persistent thoughts. A significantly higher proportion of those reporting suicidal thoughts in the past week than those reporting no suicidal thoughts in the past week reported that their thoughts were persistent and planful ( $\chi^2=19.51$ , df=3, p<.001). Planfulness and persistence were not related to grade in school, religion, past psychiatric history, or experience with suicidal behavior among family and associates.

Among the attempters, 90.3% (28 of 31) reported that they had "thought about suicide without actually trying it," 62.1% (18 of 29) reported that they had had persistent thoughts of killing themselves, and 73.3% (22 of 30) could describe a plan they had for killing themselves. Twenty-one (63.6%) of the 33 suicide attempters reported having made at least two attempts to kill themselves (range, one to six attempts) and described these attempts in detail. Overdosing and wrist slashing were the most commonly reported meth-

ods. The mean number of years from the most recent attempt was 1.2 years (range, 0–10 years). Approximately two-thirds of the attempters stated they did not tell anyone before their attempt; fewer than two-thirds stated that they told somebody after the attempt. For the first attempt, 48% (16 of 33) reported that they did not expect to die, and 24% (N=8 of 33) stated they did not know if they expected to die. Nine of 32 attempters (28.1%) reported that they had thought about killing themselves during the week before completing the survey, and 30 (8.6%) of the 34 nonattempters reported similar thoughts ( $\chi^2$ =12.17, df=2, p<.0005).

#### **DISCUSSION**

The results of this study suggest that various forms of suicidal behavior were relatively frequent among the high school students surveyed. Over 60% of the sample reported having suicidal thoughts, which varied with respect to persistence and planfulness. Most students denied having persistent suicidal thoughts. Of particular concern were the findings that almost 9% of these high school students reported having made a suicide attempt and that over half of this group made at least two attempts.

The results of this study reflect an initial attempt to describe, in detail, the spectrum of suicidal behavior in a high school sample. Since our preliminary report of the prevalence of suicide attempts in this high school sample (13), Josef et al., in an unpublished study, identified a similar prevalence rate in a larger and broader sample using an anonymous survey. Thus, it appears that high school adolescents may have a surprisingly high prevalence rate of suicide attempts, even higher than that reported for adults (1–4). Although adolescents appear ready to discuss suicidal behavior in anonymous questionnaires, we found that most suicide attempters did not tell anyone before their attempt and had not reached the attention of mental health professionals.

The ideators and attempters we described do not represent two mutually exclusive groups. Although the attempters reported more ongoing suicidal behavior than the ideators (e.g., more had suicidal thoughts in the past week and more had repeated attempts), the ideators and attempters were similar in terms of their

family history of suicidal behavior. Both had a stronger family history of suicidal behavior than those reporting no suicidal behavior.

This study is concerned primarily with adolescents attending an academically competitive high school. The results must be replicated in other high school samples and in the general community, where adolescent high school dropouts can be evaluated, before any firm conclusions about the frequency of suicidal behavior among adolescents can be made. Diagnostic and longitudinal research are also essential if we are to better understand the course of self-destructive thoughts and behaviors.

- Paykel ES, Myers JK, Lindenthal JJ, et al: Suicidal feelings in the general population: a prevalence study. Br J Psychiatry 1974; 124:460-469
- Schwab JJ, Warheit GJ, Holzer CE: Suicidal ideation and behavior in a general population. Dis Nerv Syst 1972; 33:745– 748
- Vandivort DS, Locke BZ: Suicide ideation: its relation to depression and suicide attempt. Suicide Life Threat Behav 1979; 9:205-218
- Salmons PH, Harrington R: Suicidal ideation in university students and other groups. Int J Soc Psychiatry 1984; 30:201– 205
- Pfeffer CR, Zuckerman S, Plutchik R, et al: Suicidal behavior in normal school children: a comparison with child psychiatric inpatients. J Am Acad Child Psychiatry 1984; 23:416–423
- Pfeffer CR, Conte HR, Plutchik R, et al: Suicidal behavior in latency-age children: an outpatient population. J Am Acad Child Psychiatry 1980; 19:703–710
- Pfeffer CR: Suicidal behavior of children: a review with implications for research and practice. Am J Psychiatry 1981; 138: 154-159
- Pfeffer CR, Conte HR, Plutchik R, et al: Suicidal behavior in latency-age children: an empirical study. J Am Acad Child Psychiatry 1979; 18:679–692
- Carlson GA, Cantwell DP: A survey of depressive symptoms in a child and adolescent psychiatric population. J Am Acad Child Psychiatry 1979; 18:587–599
- Smith BD, Nacev V: Drug usage as determined under conditions of anonymity and high questionnaire return rate. Int J Addict 1978; 13:725-736
- Dube KC, Kumar A, Gupta SP, et al: The question of onymity and anonymity of a questionnaire in a drug use survey. Bull Narcotics 1981; 33:45-48
- Smart RG, Blair NL: Test-retest reliability and validity of information for a high school drug use questionnaire. Drug Alcohol Depend 1978; 3:265-271
- Harkavy JM, Asnis G: Suicide attempts in adolescents: prevalence and implications (letter). N Engl J Med 1985; 313:1290

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# Augmentation of Haloperidol by Ascorbic Acid in Phencyclidine Intoxication

A. James Giannini, M.D., Robert H. Loiselle, Ph.D., Lynn R. DiMarzio, M.S., and Matthew C. Giannini, J.D.

The authors studied 40 white men with acute phencyclidine (PCP) intoxication. On a random basis, 10 were treated with ascorbic acid, 10 with placebo, 10 with haloperidol, and 10 with a combination of ascorbic acid and haloperidol. While haloperidol was significantly more effective than ascorbic acid, the combination was significantly more effective than either used alone. This combination may have a specific antipsychotic role in the emergency treatment of PCP psychosis. (Am J Psychiatry 1987; 144:1207–1209)

The treatment of acute phencyclidine (PCP) psychosis has been a two-phased affair. Initial intervention has involved the reversal of psychotic symptoms plus the rapid elimination of PCP from the patient's body. The standard treatment has been neuroleptics (1). Haloperidol has been used most successfully, supporting the view that PCP-induced psychosis is the result of increased activity of dopamine (D<sub>2</sub>) receptors (2–5).

PCP is a weak base (pKa=8.7) and is excreted renally (4). Rapid elimination is accomplished by acidification of the urine with ascorbic acid. At initial doses of 1000 mg intramuscularly, it has been reported to be successful (1).

Thus, coincidentally and independently, ascorbic acid and haloperidol have been jointly used in acute treatment of PCP psychosis (1). A review of the North American and European literature produced no studies of a possible interaction of these agents in treating PCP psychosis. However, Rebec et al. (6) did report potentiation of haloperidol activity by ascorbic acid in the treatment of amphetamine intoxication in rats. We describe here what we believe to be the first reported study of possible potentiation of haloperidol by ascorbic acid in PCP psychosis.

# **METHOD**

The subjects were 40 white men between the ages of 19 and 34 years. All had PCP intoxication. No subject included in the study had abused alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, eth-chlorvynol, glutethimide, methaqualone, phenothiazines, or tricyclics. This was verified by serum and urine analysis.

All subjects were examined before the initiation of treatment (0 minutes) with the Brief Psychiatric Rating Scale (BPRS) (7). This scale has been used in previous studies of PCP treatment (2, 3, 5). The patients were randomly assigned intramuscular doses of haloperidol (5 mg), ascorbic acid (1000 mg), haloperidol (5 mg) plus ascorbic acid (1000 mg), or placebo. Each of these four treatment groups had 10 members.

Each subject received his randomly assigned treatment at 0 minutes and 30 minutes. Ratings were conducted at 0, 30, and 60 minutes. All ratings were conducted by two psychiatry residents who were blind to the purpose of the study and the treatment.

# **RESULTS**

An intraclass correlation of .95 was obtained for interrater reliability (8). Since the interrater agreements were extremely high for all groups, the ratings were averaged for further statistical analysis. The mean of the sums of the subjects' BPRS ratings was calculated for each group at each time point; these means are presented in table 1. There were no significant differences in baseline BPRS ratings among the four treatment groups.

The mean difference between the 60- and 0-minute ratings was also calculated for each group. A linear relationship among ratings over time was found for all four groups. A two-factor analysis of variance was performed with these difference scores. The results indicated that a significant interaction effect occurred with the combined use of haloperidol and ascorbic acid (F=19.95, df=1, 36, p<.001).

The Scheffé procedure was used as a multiple comparison measure. The test showed that the combined use of haloperidol and ascorbic acid had the greatest

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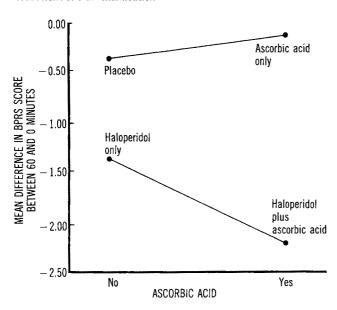
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TABLE 1. BPRS Scores of 40 Men With PCP Intoxication Treated With Ascorbic Acid, Haloperidol, a Combination, or Placeboa

		BPRS Score								
	Ascorbi	c Acid	Halope	eridol	Haloperi Ascorbi		Place	ebo		
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
0 minutes	4.37	0.20	4.35	0.20	4.37	0.20	4.30	0.20		
30 minutes	4.31	0.20	3.69	0.30	3.31	0.20	4.10	0.20		
60 minutes Difference between	4.21	0.20	2.98	0.20	2.19	0.15	3.87	0.15		
60 and 0 minutes <sup>b</sup>	-0.16	0.01	-1.37	0.10	-2.18	0.15	-0.43	0.02		

<sup>&</sup>lt;sup>a</sup>N=10 for each treatment.

FIGURE 1. Interaction Effects of Haloperidol and Ascorbic Acid in Treatment of PCP Intoxication



treatment effect. Haloperidol alone was found to be less rapid in action but to produce significant change. Placebo alone and ascorbic acid alone formed homogeneous subsets; no significant difference was found between these groups. When ranked according to mean difference, the ascorbic acid group (mean=-0.16) ranked lower than the placebo group (mean=-0.43). The multiple classification analysis indicated that 73% of the variance was accounted for by the combined use of haloperidol and ascorbic acid. The interaction effects are summarized in figure 1.

# **DISCUSSION**

The addition of ascorbic acid appears to potentiate the activity of haloperidol in counteracting PCP's effects. This finding is similar to that obtained with amphetamine-intoxicated rats. The actions of PCP and amphetamine on dopamine are similar. Both block dopamine uptake in striatal synaptosomes (1, 9). Also, both produce ataxia and stereotypy in experimental animals (10, 11), and these activities are associated with binding to striatal dopamine receptors (3). Subjectively, PCP is used as a fraudulent substitute for amphetamine in the illicit drug trade, since many abusers cannot distinguish between the effects of the two (1). Therefore, one could speculate that the observed potentiation of haloperidol by ascorbic acid may be extended to treatment of psychoses caused by all sympathomimetics.

In any case, the addition of ascorbic acid does seem to potentiate the antipsychotic activity of haloperidol in PCP psychosis in human subjects. Some controversy exists as to whether ascorbic acid inhibits binding at the dopamine receptor (12, 13). It may be that the dose of ascorbic acid we employed potentiated the effects of haloperidol, since both may operate at the same antagonist site (13, 14). Alternatively, an antioxidant action of ascorbic acid may have decreased the rate of enzymatic degradation of haloperidol (6). Ascorbic acid alone has also been reported to block amphetamine activity (12). We observed a similar effect with PCP, but ascorbic acid was less effective than the haloperidol-ascorbic acid combination or haloperidol alone. It may be that ascorbic acid acts as an acidifier. In acidifying the urine, ascorbic acid enhances the excretion of PCP by reducing the resorption from glomerular filtrate (1). The effect of ascorbic acid in such cases may be due to one of these actions, a combination, or some other mechanism.

While this study should be considered preliminary, the data strongly indicate a definite potentiation of haloperidol by ascorbic acid. If later studies support our findings, the haloperidol-ascorbic acid combination should be stressed for acute PCP intoxication. We recommend that researchers also investigate the possible utility of this combination in treating other dopamine-dependent toxic psychoses, including those caused by amphetamine and cocaine (15).

- 1. Giannini AJ, Price WA: The dissociatives: phencyclidine and phenylhexylpyrrolidine. Med Psychiatry (in press)
- 2. Giannini AJ, Kalavsky S, Loiselle RH: Possible role of the DA-2

<sup>&</sup>lt;sup>b</sup>F=19.95, df=1, 36, p<.001.

- receptor in phencyclidine psychosis. Soc Neurosci Abstr 1983; 9:33
- Giannini AJ, Eighan MJ, Giannini MC, et al: Comparison of haloperidol and chlorpromazine in the treatment of phencyclidine psychosis. J Clin Pharmacol 1984; 24:202–205
- Giannini AJ, Giannini MC, Price WA: Antidotal strategies in phencyclidine intoxication. Int J Psychiatry Med 1984; 14:315– 321
- Giannini AJ, Nageotte C, Loiselle RH, et al: Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. J Toxicol Clin Toxicol 1984–1985; 22:573–579
- Rebec GV, Centore JM, White LK, et al: Ascorbic acid and the behavioral response to haloperidol: implication for the action of antipsychotic drugs. Science 1985; 227:438-440
- 7. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799-812
- 8. Winer BJ (ed): Statistical Principles in Experimental Design, 2nd ed. New York, McGraw-Hill, 1971, p. 184
- Smith RC, Meltzer HY, Arora RC, et al: Effects of phencyclidine on [3H]catecholamine and [3H]serotonin uptake in

- synaptosomal preparations from rat brain. Biochem Pharmacol 1977; 26:1435–1439
- Castellani S, Giannini AJ, Adams PM: Effects of naloxone, metenkephalin and morphine on phencyclidine-induced behavior in the rat. Psychopharmacology (Berlin) 1982; 78:76-80
- Cole SO: Brain mechanisms of amphetamine induced anorexia, locomotion and stereotypy. Neurosci Biobehav Rev 1978; 2: 89–100
- 12. Heikkila RE, Cabbat FS, Manzino L: Differential inhibitory effects of ascorbic acid on the binding of dopamine agonists and antagonists on neostriatal membrane preparations. Res Commun Chem Pathol Pharmacol 1985; 34:409–421
- 13. Hajdiconstantinou M, Neff NH: Ascorbic acid could be hazardous to your experiments: a commentary on dopamine receptor binding studies with speculations on a role for ascorbic acid in neuronal function. Neuropharmacology 1983; 22:939–943
- Leff S, Sibley DR, Hamblin M, et al: Ascorbic acid enables reversible dopamine receptor <sup>3</sup>H-agonist binding. Life Sci 1981; 29:2081–2090
- Giannini AJ, Malone DA, Giannini MC, et al: Treatment of cocaine and phencyclidine abuse. J Clin Pharmacol 1986; 26: 211-214

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# Survivors of Imprisonment in the Pacific Theater During World War II

Gerald Goldstein, Ph.D., Welmoet van Kammen, Ph.D., Carolyn Shelly, M.A., David J. Miller, Ph.D., and Daniel P. van Kammen, M.D., Ph.D.

Data were obtained from 41 survivors of imprisonment by the Japanese during World War II. Interview data suggested that these individuals, despite the 40 years that had passed since their prisoner of war experiences, showed manifestations of posttraumatic stress disorder, notably a sleep disturbance marked by recurrent nightmares. MMPI data suggested significant pathology, characterized as an anxiety state, in this group. Half of the subjects met the full set of DSM-III criteria for posttraumatic stress disorder.

(Am J Psychiatry 1987; 144:1210-1213)

R eports on the psychopathology of former prisoners of war (POWs) have emphasized the longterm effects of stressful experience. Studies comparing former POWs with suitable control subjects have reported greater frequency of psychiatric illness (1–3) among POWs, as well as higher disability ratings (2) and significant pathology on neuropsychological and psychiatric assessments (4, 5). Psychiatric symptoms frequently reported include depression, anxiety, sleep disturbance, impaired memory, and social isolation (6). There is evidence that duration of captivity appears to influence symptom severity (2, 4) and that the severity of the stressor, rather than the existence of predisposing personality characteristics, is the more crucial factor with regard to the development of posttraumatic psychiatric syndromes (7). Because many POWs have been exposed to physical brutality as well as extreme mental stress, the nature of their experiences as well as the psychiatric sequelae are in many respects similar to those described among survivors of Nazi persecution (8, 9) and, more recently, among survivors of Cambodian concentration camps

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The symptoms characteristic of individuals with histories of wartime imprisonment or concentration camp experience would now be conceptualized in terms of the DSM-III diagnosis of posttraumatic stress disorder. DSM-III classifies posttraumatic stress disorder as an anxiety disorder and has established diagnostic criteria for it. The disorder is thought to have three major features, including continued reexperiencing of the traumatic event, reduced social involvement, and a number of anxiety-related symptoms, notably sleep disturbance. The diagnosis of posttraumatic stress disorder is most commonly associated with the Vietnam experience, and the establishment of its descriptive validity has been based mainly on studies of Vietnam veterans (11, 12). Related studies have looked at concomitant psychopathology (13) in individuals with posttraumatic stress disorder, as well as family histories of such individuals (14). It is only recently that studies involving the diagnosis of posttraumatic stress disorder have focused on combat veterans of World War II (15) and the Korean conflict (16).

Several studies of posttraumatic stress disorder have used various objective assessment instruments, notably the MMPI. An MMPI scale has been developed that has been shown to accurately diagnose posttraumatic stress disorder (17). Various comparisons have been made between Vietnam veterans with or without posttraumatic stress disorder; one study (18) reported a relationship between both severity of combat exposure and military adjustment and posttraumatic stress disorder, and another (19) reported numerous significant differences between the two groups on the MMPI. It has also been noted that veterans diagnosed as having posttraumatic stress disorder produced MMPI profiles that did not differ significantly from those obtained by a random sample of psychiatric patients newly admitted to a Veterans Administration (VA) facility (19). Perhaps most relevant to the present investigation was a study in which the MMPI was administered to groups of ex-POWs who served in the Pacific theater during World War II (20). The mean MMPI profile obtained in that study greatly resembled what was found in Vietnam veterans by Fairbank et al. (17) and, as will be seen, in our own sample.

The present study reports on preliminary psychiatric findings in a group of veterans, all of whom had fought

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during World War II in the Pacific theater, mainly in the battles of Bataan and Corregidor. These defenders of Bataan and Corregidor were all captured and held prisoner by the Japanese for over 31/2 years. It is well-known that POWs in the Pacific theater during World War II typically experienced extremely inhumane and brutal treatment. The individuals in this study have provided numerous accounts of such experiences. All but two of them participated in the 1942 Bataan Death March and were transported to Japan in what are described as "hell ships" to work in mines and factories. The two who were not on the Bataan Death March were captured later but were also imprisoned in Japan for lengthy periods. It has been recorded that of the 35,000 servicemen captured by the Japanese, only 22,000 survived and returned home to the United States.

These individuals came to our attention primarily because of recent legislation that, among other benefits, entitled them to a comprehensive general medical and psychiatric evaluation, to be accomplished by the VA. On psychiatric evaluation, these subjects almost universally reported psychiatric symptoms strongly suggestive of certain aspects of chronic posttraumatic stress disorder. Most prominent among the symptoms was sleep disturbance, manifested largely by recurrent dreams of the event. Many subjects also reported persistent flashbacks, hyperalertness, and sensitivity to events and stimuli that reminded them of their experiences as POWs. The subjects' reports were of particular interest, since it was some 40 years after their liberation when they were examined, and the symptoms apparently had persisted for all of that time. Nevertheless, after their liberation these individuals typically maintained successful careers and stable family lives. Many of them are now retired after many years of steady employment. They therefore constitute a group with significant psychopathology but with sufficient personal resources to cope with it, and they live relatively normal lives from the point of view of work and family considerations.

# **METHOD**

The sample consisted of 41 defenders of Bataan and Corregidor. Their mean±SD age was 64.56±3.55 years, and they had a mean of 12.20±2.53 years of education. They were all community dwellers who came to a VA facility as participants in a comprehensive evaluation service established for ex-POWs. None of them required current hospitalization for medical or psychiatric illness, nor did many of them have significant medical or psychiatric histories except for the immediate sequelae of their experience as prisoners. Thus, some of them had histories of malaria, various malnutrition syndromes such as beriberi, and related disorders. While some subjects had complaints, most of which were somatic in nature, very few had sought psychiatric treatment.

TABLE 1. Psychosocial Characteristics of Former World War II Prisoners of War

	Available		cts With
Characteristic	N	N	%
Criminal record	38	2	5.3
Current problem drinking Prior history of problem	38	8	21.1
drinking or substance abuse	37	6	16.2
Marital status <sup>a</sup>	37		
Currently married		27	73.0
Widowed and remarried		3	8.1
Divorced and remarried		3 3 2	8.1
Widowed		2	5.4
Divorced		2	5.4
Number of divorces	37		
None		32	86.5
One		4	10.8
Two		1	2.7
Employment status <sup>b</sup>	37		
Currently working		4	10.8
Retired		31	83.8
Discharged		2	5.4

<sup>&</sup>lt;sup>a</sup>Mean±SD years of marriage=36.87±6.51.

As part of the evaluation, each subject was given a semistructured psychiatric interview and the MMPI. The interview was conducted by a Board-certified psychiatrist and was directed primarily toward elicitation of any symptoms of posttraumatic stress disorder and related disorders. The psychiatric interview protocols were reviewed, and the subjects were rated for each of the criteria for posttraumatic stress disorder listed in DSM-III (e.g., recent and intrusive recollections of the event). These criteria were rated as present or absent. The sample's mean MMPI profile was also computed. Psychosocial data were collected during the psychiatric interview and also through examination of records and follow-up contacts with subjects when additional information was required. The aim of the evaluation was to determine the extent to which subjects were living normal, productive lives despite the POW experience and subsequent psychopathology. The information obtained by interview, record review, or follow-up contact was categorized with regard to history of psychiatric treatment, history of criminality, problem drinking or other substance abuse, and work and marital histories.

# RESULTS

The psychosocial data are summarized in table 1. With regard to history of psychiatric treatment, none of the eight inpatient hospitalizations was for a psychiatric reason. All but six of the subjects had had some outpatient treatment, but in 21 cases, this treatment was given after the subject was called in for the ex-POW examination and was specifically recommended because of the findings noted on psychiatric

bMean±SD years of employment=30.58±4.99.

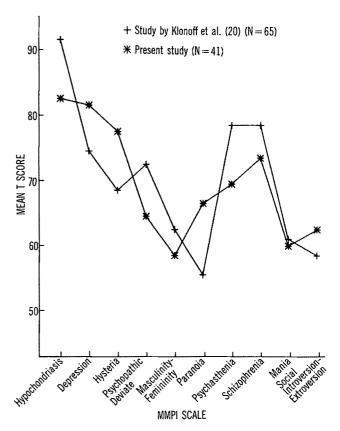
TABLE 2. Symptoms of DSM-III Posttraumatic Stress Disorder Among 32 Former World War II Prisoners of War

	Sul	bjects
Symptom	N	%
Sleep disturbance	31	96.9
Recurrent dreams of the event	30	93.8
Recurrent and intrusive recollections of the event Feeling of detachment or estrangement from	23	71.9
others	20	62.5
Memory impairment or trouble concentrating Intensification of symptoms by exposure to events that symbolize or resemble the traumatic event	19 12	59.4 37.5
Hyperalertness or exaggerated startle response	7	21.9
Sudden acting or feeling as if the traumatic event were recurring	8	25.0
Avoidance of activities that arouse recollection of the traumatic event Guilt about surviving or about behavior required	7	21.9
for survival	6	18.8
Constricted affect	5	15.6
Markedly diminished interest in one or more		
significant activities	3	9.4

evaluation. Mean±SD years of outpatient treatment were 3.89±5.28 (N=37). Only three subjects reported a lengthy history of outpatient treatment. Very few of the subjects had criminal records. A total of 14 subjects (34%) had a history of problem drinking; only eight of them (20%) were drinking at the time of the evaluation. In no case was severity of problem drinking sufficient to interfere with social or occupational functioning, nor did any of the subjects have current DSM-III diagnoses of alcohol abuse or dependence. There were no other forms of active substance abuse found in the sample. One subject had been addicted to morphine in the past but had resolved the addiction by the time of our evaluation.

The psychiatric interview data are presented in terms of the criteria for posttraumatic stress disorder listed in DSM-III (see table 2). It will be noted that not all of the subjects manifested the full syndrome; only half of them met the full set of criteria required for a diagnosis of posttraumatic stress disorder. However, most reported recurrent recollections of their period of imprisonment and a sleep disturbance manifested by nightmares involving their imprisonment experience. Most of them reported interpersonal detachment and memory and concentration difficulties. Very few subjects reported constricted affect or loss of interest in significant activities. This pattern is quite consistent with the social histories of most subjects in that they tended to be involved, active people for most of their lives. The memory and concentration difficulties may be largely attributable to aging, and, indeed, several of them reported what appeared to be age-related memory problems. In summary, as a group they appeared to maintain the emotional sequelae, but not some of the active symptoms (e.g., hyperalertness, survivor guilt, and acting as if the traumatic event was actually recurring), of their imprisonment experience. Sleep

FIGURE 1. MMPI Profiles for Former World War II Prisoners of War in Two Studies



disturbances were almost universal among the subjects.

The sample's mean MMPI profile is presented in figure 1. It is characterized by elevations on the hypochondriasis, depression, and hysteria scales, the combination of which suggests the presence of a pronounced anxiety state with depressive features. We also conducted an examination of individual MMPI items and found that items endorsed by more than half of the subjects related to sleep disturbance (e.g., "I have nightmares every few nights") and somatic concerns (e.g., "I seldom worry about my health" [answered "false"]). These results are comparable to those of Klonoff et al. (20), who administered the MMPI to groups of ex-POWs who had served in the Pacific theater during World War II. Their evaluation was done approximately 10 years before ours, and so their subjects were in their 50s at the time of testing. Nevertheless, it seemed useful to compare our data with theirs, so the mean MMPI profile for their subjects is also presented in figure 1.

# **DISCUSSION**

This preliminary, descriptive study of survivors of lengthy imprisonment under extremely stressful conditions appears to have produced a number of possibly important findings. First, despite the passage of about 40 years since the traumatic experience, most of the individuals studied continued to have symptoms apparently related to it. The most common of these symptoms were flashbacks or recurrent memories of the experience and a sleep disturbance manifested by nightmares with themes revolving around the period of imprisonment. Several of the subjects phrased the matter in terms of never having had a good night's sleep since they were liberated. The symptom pattern bears some resemblance to the *DSM-III* description of posttraumatic stress disorder, but half of the subjects did not appear to have the full syndrome.

The MMPI data revealed that these individuals generally had great concern for their physical health, a characteristic that is not a component of posttraumatic stress disorder. At least to some extent, this concern may be realistic. Many of these individuals developed various nutritional, infectious, and orthopedic disorders during their period of imprisonment and were possibly realistically concerned about long-term consequences. In addition, some, but not the majority, of the subjects suffered from the more classic symptoms found in ex-POWs and individuals with posttraumatic stress disorder, such as hyperalertness, survivor guilt, and the reliving of certain aspects of their war experiences when exposed to similar events. For example, some of them reported becoming distressed when they saw war movies or were in the presence of Orientals.

Perhaps of greatest interest is that while these individuals provided both historical and psychometric evidence of significant psychopathology, comparable in some respects to Vietnam veterans with posttraumatic stress disorder, they nevertheless lived relatively successful and effective lives, albeit with the discomforts and limitations imposed by their disorder. The only major adjustment difficulty found was that about a third of the subjects had some history of problem drinking. Thus, while perhaps demonstrating the reality of the diagnosis of posttraumatic stress disorder, the data suggest that at least a form of the disorder is characterized more by internalized anxiety than by the more well-known acting out characteristics of some forms of posttraumatic stress disorder.

# **REFERENCES**

1. Beebe GW: Follow-up studies of World War II and Korean War prisoners, II: morbidity, disability and maladjustments. Am J

- Epidemiol 1975; 107:400-422
- Cohen BM, Cooper MZ: A follow-up study of World War II prisoners of war. VA Medical Monograph 1954, pp 1--71
- 3. Sutker PB, Winstead DK, Goist KC, et al: Psychopathology subtypes and symptom correlates among former prisoners of war. J Psychopathol Behav Assess 1986; 8:89–101
- 4. Klonoff H, McDougall G, Clark C, et al: Neuropsychological, psychiatric, and physical effects of prolonged and severe stress: 30 years later. J Nerv Ment Dis 1976; 163:247–252
- Kluznik JC, Speed N, VanValkenburg C, et al: Forty-year follow-up of United States prisoners of war. Am J Psychiatry 1986; 143:1443–1446
- Segal J, Hunter EJ, Segal Z: Universal consequences of captivity: stress reactions among divergent populations of prisoners of war and their families. Int Soc Sci J 1976; 28:593

  –609
- Ursano RJ, Boydstun JA, Wheatley RD: Psychiatric illness in US Air Force Viet Nam prisoners of war: a five-year follow-up. Am J Psychiatry 1981; 138:310–314
- Dor-Shav NK: On the long range effects of concentration camp internment on Nazi victims. J Consult Clin Psychol 1978; 46:1– 11
- 9. Eitinger L: Pathology of the concentration camp syndrome: preliminary report. Arch Gen Psychiatry 1961; 5:371-379
- Kinzie JD, Fredrickson RH, Ben R, et al: Posttraumatic stress disorder among survivors of Cambodian concentration camps. Am J Psychiatry 1984; 141:645–650
- Frye JS, Stockton RA: Discriminant analysis of posttraumatic stress disorder among a group of Viet Nam veterans. Am J Psychiatry 1982; 139:52–56
- Silver SM, Iaconi CU: Factor-analytic support for DSM-III's post-traumatic stress disorder for Vietnam veterans. J Clin Psychol 1984; 40:5–14
- Streimer JH, Cosstick J, Tennant C: The psychosocial adjustment of Australian Vietnam veterans. Am J Psychiatry 1985; 142:616–618
- Roberts WR, Penk WE, Gearing ML, et al: Interpersonal problems of Vietnam combat veterans with symptoms of posttraumatic stress disorder. J Abnorm Psychol 1982; 91:444– 450
- Van Dyke C, Zilberg NJ, McKinnon JA: Posttraumatic stress disorder: a thirty-year delay in a World War II veteran. Am J Psychiatry 1985; 142:1070–1073
- Thienes-Hontos P, Watson CG, Kucala T: Stress-disorder symptoms in Vietnam and Korean war veterans. J Consult Clin Psychol 1982; 50:558–561
- Fairbank JA, Keane TM, Malloy PF: Some preliminary data on the psychological characteristics of Vietnam veterans with posttraumatic stress disorder. J Consult Clin Psychol 1983; 51:912– 919
- 18. Foy DW, Sipprelle RC, Rueger DB: Etiology of posttraumatic stress disorder in Vietnam veterans: analysis of premilitary, military, and combat exposure influences. J Consult Clin Psychol 1984; 52:79–87
- 19. Burke H, Mayer S: The MMPI and the post-traumatic stress syndrome in Vietnam era veterans. J Clin Psychol 1985; 41: 152–156
- Klonoff H, Clark C, Horgan J, et al: The MMPI profile of prisoners of war. J Clin Psychol 1976; 32:623–627

# Clinical and Research Reports

# Increased Adrenal Weight in Victims of Violent Suicide

Katerina Dorovini-Zis, M.D., F.R.C.P.(C), and Athanasios P. Zis, M.D., F.R.C.P.(C)

Adrenal weight was significantly higher in 16 victims of violent suicide than in 10 subjects who died suddenly from other causes. Since approximately half of suicide victims are depressed, these results support an association between depression and hypertrophy of the adrenal cortex. (Am J Psychiatry 1987; 144:1214–1215)

S ince the original observation by Gibbons (1) nearly a quarter of a century ago, several studies have documented that a substantial number of depressed patients hypersecrete cortisol. It has been hypothesized (2) that a hypothalamic-limbic system disturbance resulting in hypersecretion of ACTH is responsible for the hypercortisolemia present in depression. The adrenal cortisol response to ACTH is believed to remain essentially normal (3). This assumption is supported by the fact that most, but not all, of the earlier studies reported no change associated with depression in the adrenal cortisol response to ACTH (3). In a more recent study (4), however, the administration of an intravenous bolus of cosyntropin (ACTH $\alpha_{1-24}$ ) caused significantly higher cortisol concentrations and earlier peak responses in patients with endogenous depression than in normal subjects. Consistent with these results is the observation that depressed patients show a

proportionally greater cortisol response to a given amount of ACTH released during stimulation with corticotropin-releasing factor than do normal control subjects (5). To explain these observations, it has been suggested (5) that there is a progressive anatomical and functional hypertrophy of the adrenal cortex in response to chronic hyperstimulation by ACTH during the course of depression. We report here data consistent with this hypothesis.

# **METHOD**

The experimental material consisted of adrenal glands taken at the time of autopsy from 16 subjects who committed violent suicide and died immediately between March 1, 1986, and Oct. 31, 1986. The group included 12 men and four women, and their mean  $\pm$ SD age was  $43.7\pm16.2$  years. The methods of suicide were jumping (N=7), hanging (N=4), shooting (N=4), and suffocation (N=1).

The control material consisted of the adrenal glands taken at the time of autopsy from 10 individuals who had died suddenly from violent or natural causes over the same period of time. They included six men and four women aged  $44.0\pm17.1$  years. Subjects with a known history of psychiatric illness were excluded from this group. The causes of death were motor vehicle accident (N=4), other trauma (N=2), ruptured berry aneurysm (N=2), and acute coronary insufficiency (N=2).

After removal of the adrenal glands from the body, the surrounding fat was carefully cut away from the capsule, each adrenal gland was separately weighed, and the combined weight of both glands was recorded. The cause of death was recorded independently of the adrenal weight measurement and was taken from the completed autopsy report. Potential subjects with severe, protracted, or debilitating illness were excluded from the study.

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# **RESULTS**

The mean ±SD combined weight of both adrenal glands was significantly higher for the suicide group  $(9.77\pm1.74 \text{ g})$  than for the control group  $(7.74\pm0.82 \text{ g})$ g) (t=4.05, df=22.75, p<.001; t test for unequalvariance, two-tailed). There was considerable variation in the adrenal weight of the subjects who had committed suicide: the combined weight of both adrenal glands of four subjects was greater than 11 g, whereas in another four subjects it was less than 8 g. The combined weight in nine suicide victims, however, was greater than the highest value obtained in the control group. There was no relationship between adrenal weight and age at death (r=.00, df=25, n.s.), nor was there a significant difference in adrenal weight between men and women (t=1.26, df=24, n.s.). The relationship between adrenal and total body weight was not statistically significant (r=.36, df=23, n.s.), nor was there a significant difference in total body weight between the suicide (N=15) and control (N=9)groups (mean±SD=73.0±12.8 and 71.6±10.8 g, respectively).

# **DISCUSSION**

To our knowledge, an increase in the adrenal weight of suicide victims has not been documented before. This observation, although of considerable interest, is from our preliminary work in this field. At this stage we did not conduct a post-mortem review of each subject's psychiatric history but limited our investigation to a review of the autopsy reports. The information in many cases was not complete or reliable enough to warrant a statement regarding the presence and duration of specific psychiatric syndromes before the suicide. Therefore any conclusions regarding an association between depression and increased adrenal weight must be considered tentative.

The average weight of an adrenal gland from a normal adult is approximately 4.0 g. This figure is based on the careful examination of adrenal glands from adults who died suddenly without prior illness (6, 7). Nearly 90% of the gland's weight is accounted for by the cortex. No significant differences in the mean weights of the left and right glands have been recorded. Adrenal weight does not appear to be affected by body weight, sex, or age (6–8). In view of the observation that the average adrenal weight of patients undergoing adrenalectomy for metastatic breast carcinoma is also approximately 4.0 g, significant physiological enlargement is considered to occur only during severe and/or prolonged stress (6, 7).

It has been estimated by careful post-mortem psychiatric investigations that most of the subjects who commit suicide are mentally ill (9, 10). Of those with psychiatric disturbances, 40% to 60% suffer from depression (9, 10). It is plausible that the proportion of mentally ill subjects in our sample was similar to that reported in the literature. Considering that none of our subjects was suffering from a severe, protracted, or debilitating physical ailment at the time of death, we also assume that the observed increase in adrenal weight in our suicide group is largely accounted for by the preexisting psychiatric morbidity. This is compatible with the well-established phenomenon of progressive hypertrophy of the adrenal gland during chronic stress (6, 7). Our results are also consistent with reports of an exaggerated adrenal cortisol response to exogenous or endogenous ACTH in depressed patients (4, 5) and with the hypothesis that during the course of depression there is a progressive functional and anatomical hypertrophy of the adrenal gland in response to chronic hyperstimulation by ACTH (5). The observed variability in the adrenal weight of suicide victims could be the result of differences in the nature and duration of the psychiatric morbidity preceding the suicide. Since, however, we did not conduct a post-mortem psychiatric investigation and did not consider the data in the autopsy report sufficient to ascertain a psychiatric diagnosis, this remains to be shown.

- Gibbons JL: Cortisol secretion rate in depressive illness. Arch Gen Psychiatry 1964; 10:572–575
- Carroll BJ, Curtis GC, Mendels J: Neuroendocrine regulation in depression, I: limbic system-adrenocortical dysfunction. Arch Gen Psychiatry 1976; 33:1039–1044
- Carroll BJ, Mendels J: Neuroendocrine regulation in affective disorders, in Hormones, Behavior and Psychopathology. Edited by Sachar EJ. New York, Raven Press, 1976
- Amsterdam JD, Winokur A, Abelman E, et al: Cosyntropin (ACTHα<sub>1-24</sub>) stimulation test in depressed patients and healthy subjects. Am J Psychiatry 1983; 140:907–909
- Gold PW, Chrousos G, Kellner C, et al: Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. Am J Psychiatry 1984; 141:619–627
- Symington T: Functional Pathology of the Human Adrenal Gland. Edinburgh, ES Livingstone, 1969
- Neville AM, O'Hare MJ: The Human Adrenal Cortex. Berlin, Springer-Verlag, 1982
- Gelfman NA: Morphologic changes of adrenal cortex in disease. Yale J Biol Med 1964; 37:31-54
- Robins E, Murphy GE, Wilkinson RH, et al: Some clinical considerations in the prevention of suicide based on a study of 134 successful cases. Am J Public Health 1959; 49:888–898
- 10. Barraclough B, Bunch J, Nelson B, et al: A hundred cases of suicide: clinical aspects. Br J Psychiatry 1974; 125:355–379

# Increased Ventricle-to-Brain Ratio in Late-Onset Schizophrenia

Peter Rabins, M.D., M.P.H., Godfrey Pearlson, M.B.B.S., Geetha Jayaram, M.D., Cynthia Steele, R.N., and Larry Tune, M.D.

For 29 patients with schizophrenia that began after age 44, the mean ventricle-to-brain ratio was significantly higher than for 23 age-matched normal subjects but significantly smaller than for 23 patients with Alzheimer's disease and hallucinations or delusions.

(Am J Psychiatry 1987; 144:1216–1218)

The finding that a subgroup of schizophrenic patients have enlarged ventricles according to CAT head scans was first reported by Johnstone et al. (1) and has been widely replicated (1, 2). Most of the subjects in these studies had clinical onsets before age 45, in part because one *DSM-III* criterion excludes a diagnosis of schizophrenia if the symptoms began after age 44.

The basis for limiting the diagnosis of schizophrenia to cases with onsets before age 45 is not clear. While it is well established that the median age at the onset of treated schizophrenia is 15–24 years for males and 25–34 years for females (3) and that the incidence drops off sharply after age 45 even when late onset is not excluded (3), many studies (4–7) have demonstrated similarities in phenomenology, course, and treatment response between the early- and late-onset conditions. To our knowledge, no study has examined ventricular size in late-onset schizophrenia.

# **METHOD**

All charts of patients aged 60 and older who were hospitalized with hallucinations and/or delusions and were admitted to the Henry Phipps Psychiatric Clinic

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between January 1983 and February 1986 were reviewed. We identified 29 individuals who 1) met the DSM-III criteria for schizophrenia except for onset after age 44 and 2) each had a nonenhanced CAT head scan with either a Siemens Somatom DR-3 (N=10) or AS&E scanner (N=19). The slices were 8 mm thick at 0° to the supraorbitomeatal line. No CAT scan showed evidence of stroke, focal change, or a space-occupying lesion. The ventricle-to-brain ratio (VBR) was determined on the cut passing through the widest portion of the bodies of the lateral ventricles with a computer-driven digitizing planimeter (8).

Each subject was cognitively normal at the time of scan and had a Mini-Mental State examination score higher than 24. Subjects were excluded if they had histories of alcohol or drug abuse, hypertension, steroid treatment, significant head trauma, or other diagnosable mental disorders. Descriptive information was obtained from the standardized chart information sheet described elsewhere (2). Of the 29 patients with late-onset schizophrenia, 26 (90%) were female and three were male. Their current mean±SD age was 73.0±7.4 years, and their age at the onset of symptoms was  $66.4\pm10.1$  years. Sixteen patients (55%) were black. Nine (31%) each had at least one of Schneider's first-rank symptoms. All subjects were being treated with neuroleptic drugs, and 25 (86%) were described by their clinicians as having partial or full responses. Twelve (41%) each had one or more documented clinically significant visual or auditory impairment. These 29 patients were compared with 41 patients with similar symptoms who also met the DSM-III criteria for schizophrenia except onset after age 44 and were treated during the same period of time but did not undergo CAT head scans. This group had a similar age at onset (62.4±10.7 years; t=1.55, df=68, n.s.), percentage of female subjects (83%;  $\chi^2$ =0.62, df=1, n.s.), and prevalence of sensory impairment (24%;  $\chi^2$ =2.27, df=1, n.s.).

A comparison group of 23 age-appropriate normal subjects was constructed from 153 screened individuals who were neurologically and cognitively normal. The comparison subjects were aged 60–83 years and were referred to in a previous publication (8). They had none of the exclusionary criteria already listed. As described previously (8), 40 of the 153 normal subjects were scanned with the AS&E scanner and 113 had scans with the Siemens machine. According to analysis of

TABLE 1. Ventricle-to-Brain Ratio (VBR) and Age of Normal Subjects, Patients With Late-Onset Schizophrenia, and Patients With Alzheimer's Disease and Hallucinations or Delusions

		Age (years)		VBR (%)	
Group	N	Mean	SD	Mean	SD
Normal control subjects Patients with late-onset	23	72.1	6.4	8.6	5.2
schizophrenia Patients with probable Alzheimer's disease and	29	73.0	7.4	13.3ª	3.4
hallucinations or delusions	23	71.9	5.7	17.5 <sup>b</sup>	5.0

<sup>&</sup>lt;sup>a</sup>Significantly different from VBR of normal subjects (t=4.75, df=50, p<.001) or Alzheimer's disease patients (t=4.16, df=50, p<.001) (post hoc Scheffé tests).

bSignificantly higher than VBR of normal subjects (t=8.90, df=44, p<.001; post hoc Scheffé test).

variance (ANOVA), scanner type had no effect on VBR (8).

A second comparison group consisted of 23 agematched patients with probable Alzheimer's disease; they were diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, and each had a Mini-Mental State score lower than 24. They attended the Johns Hopkins Department of Psychiatry Dementia Research Clinic and were determined by the examining psychiatrist to have coexisting hallucinations and/or delusions. These individuals were scanned with the same AS&E (N=10) or Siemens (N=13)machines and the same scan variables. No difference in VBR (%) between the two scanners was seen in the current group  $(18.3\pm4.3 \text{ and } 16.6\pm4.4, \text{ respectively};$ t=0.91, df=27, n.s.).

Informed consent was obtained from all subjects except for the Alzheimer's disease patients. For that group, informed consent was given by family members when the patient was unable to consent.

# RESULTS

There were no significant differences in age among the three groups. An ANOVA revealed statistically significant differences for the main effect of group (diagnosis) on VBR (F=44.3, df=72, 2, p<.01). As can be seen in table 1, the schizophrenic group had ventricles larger than those of the age-appropriate normal subjects but smaller than those of the Alzheimer's disease patients with delusions or hallucinations. Of the 29 late-onset schizophrenic subjects, 25 had VBRs higher than the mean for the age-matched normal cohort. Four (14%) of the schizophrenic patients exceeded previously calculated decile-matched normal values (8) by two or more standard deviations. The mean VBR of the 23 age-appropriate normal subjects was significantly lower than that of the lateonset schizophrenic sample (see table 1). There was no significant difference in VBR (%) between the lateonset schizophrenic patients examined with the AS&E scanner (13.6±2.52) and those examined with the Siemens scanner (12.9±3.4) (t=0.63, df=27, n.s.). We therefore felt justified in combining the data obtained with the two scanners.

# **DISCUSSION**

This study demonstrates that patients whose schizophrenia began after age 44 have a mean VBR that is higher than that of age-matched normal subjects but lower than that of age-matched demented individuals. Increased VBR is a nonspecific marker with a variety of possible etiologies, including birth trauma, degenerative brain disease, and neuroleptic use. However, since the ratio of the VBR of the late-onset schizophrenic patients to the VBR of the age-appropriate normal subjects was 1.55, similar to the ratio of 1.56 found for younger schizophrenic patients and ageappropriate normal subjects (9), we believe it unlikely that this difference in the schizophrenic patients was a manifestation of an early progressive dementia of the Alzheimer type. However, that possibility cannot be ruled out because we do not have systematic long-term follow-up data on all patients. However, previous follow-up studies (4, 10) have not found a progression to dementia.

This study did not address the question of why these individuals develop schizophrenia late in life. Many authorities (6) suggest that schizophrenia has multiple causes, and it remains possible that the late- and early-onset disorders have different etiologies. Indeed, many studies (4–7, 10) have found less genetic loading, more hearing loss, and a higher proportion of females among the late-onset group. Prospective longitudinal studies of early- and late-onset cases could identify factors that délay onset (6), but most studies, including the present one, have been retrospective.

Much of the skepticism about the existence of late-onset schizophrenia comes from its low prevalence. In our previous study (7), late-onset schizophrenia was diagnosed in only 2.7% of admitted psychiatric patients over age 44. Nonetheless, further study of this uncommon disorder may provide insight into the causes and underlying neurobiology of schizophrenia whatever the age at onset.

- Johnstone EC, Crow TJ, Husband J, et al: Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 1976; 2:924–926
- Pearlson GS, Garbacz DJ, Moberg PJ, et al: Symptomatic, familial, perinatal, and social correlates of computerized axial tomography (CAT) changes in schizophrenics and bipolars. J Nerv Ment Dis 1985; 173:42-50
- Eaton WE: Epidemiology of schizophrenia. Epidemiol Rev 1985; 7:105–126
- Roth M: The natural history of mental disorder in old age. J Ment Sci 1955; 101:281–301
- 5. Post F: Persistent Persecutory States of the Elderly. London,

Pergamon Press, 1966

- Kay DW, Roth M: Environmental and hereditary factors in the schizophrenias of old age ("late paraphrenia") and their bearing on the general problem of causation in schizophrenia. J Ment Sci 1961; 107:649-686
- Rabins PV, Pauker S, Thomas J: Can schizophrenia begin after age 44? Compr Psychiatry 1984; 25:290–294
- 8. Pearlson GD, Tune LE: Cerebral ventricular size and cerebro-
- spinal fluid acetylcholinesterase levels in senile dementia of the Alzheimer type. Psychiatry Res 1986; 17:23–29
- Pearlson GD, Kim WS, Kubos KL, et al: VBR, CT density, brain area and cranial size in 50 schizophrenics. Arch Gen Psychiatry (in press)
- Jorgensen P, Munk-Jorgensen P: Paranoid psychosis in the elderly: a follow-up study. Acta Psychiatr Scand 1985; 72:358– 363

# Association of Elevated Plasma Anticholinergic Activity With Delirium in Surgical Patients

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In a surgical intensive care unit, plasma anticholinergic activity was significantly higher in nine delirious patients than in 16 patients without delirium. The delirium may have been related to medications that are known to be associated wth delirium and/or anticholinergic activity.

(Am J Psychiatry 1987; 144:1218–1220)

Delirium is prevalent among hospitalized patients and is often unrecognized by physicians (1, 2). Among medical and oncology patients, it is associated with a high mortality rate (3, 4), and it probably contributes considerably to morbidity as well as to mortality among surgical patients (5). Psychiatric evaluation of hospitalized surgical patients seen in consultation at our institution revealed that delirium was present in 20.7% of them (6). A study of postcardiotomy delirium revealed a strong relationship between serum anticholinergic activity and cognitive impairment (7).

In the present study, we determined the presence of delirium among patients in a surgical intensive care unit, estimated the risk of delirium by using the

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drug-risk number developed by Summers (8), and measured plasma anticholinergic activity.

# **METHOD**

Mental status examinations were given by one of us (R.C.G.) to 25 patients in the surgical intensive care unit over a 3-month period. Patients were studied on four separate mornings, approximately 3 weeks apart, to ensure a representative sample. Examinations were done for all patients who were present in the unit 1) who had not been previously interviewed, 2) who had not received general anesthesia during the preceding 24 hours, 3) from whom blood samples had been obtained within 4 hours before the mental status examination as part of routine arterial blood gas monitoring, and 4) who were alert enough to respond to verbal communication. There were 18 men and seven women in the study; their average age was 58.1 years (range=29-76 years). Twenty-four patients had had major surgical operations (10 cardiac, four gastrointestinal, four vascular, one genitourinary, two renal transplant, one thoracic, and two other) before admission to the surgical intensive care unit. The remaining two patients were admitted for nonsurgical treatment of inflammatory conditions.

The presence or absence of delirium was determined after mental status examination according to *DSM-III* criteria.

Blood was placed in sterile collection tubes containing lithium heparin. Assay for plasma anticholinergic activity was performed on each sample by a radio-

TABLE 1. Drug Doses Used in Calculating Risk of Delirium in Surgical Patients

Drug	Level 2 Dose Range (mg/day)
Class I (known synergistic effect with	
anticholinergic agents, but not known	
to be a direct cause of delirium)	0
Class II (known to cause delirium but	-
currently not documented to have CNS	
anticholinergic properties)	
Acetylsalicylic acid	1800-6000
Codeine	60–180
Dexamethasone	0.5-20
Digoxin	0.125-0.375
Dopamine <sup>b</sup>	312_0 31373
Hydralazine	100-200
Hydrocortisone <sup>c</sup>	100-1200
Hydroxyzine	100-400
Labetalol <sup>c</sup>	400-800
Methylprednișolone <sup>c</sup>	4-48
Nitroprusside <sup>b</sup>	
Prednisolone <sup>c</sup>	5-60
Prednisone	5-60
Procainamide	2000-4000
Propranolol	40-160
Ranitidine <sup>c</sup>	100-300
Class III (known to cause delirium reversed	
by CNS active anticholinesterases or	
known to have CNS anticholinergic effect	
and to cause delirium	
Diazepam	5-20
Diphenhydramine	125-250
Meperidine	200-900
Morphine sulphate	25-50
Nortriptyline	25-50
Phenobarbital	100-320
Triazolam <sup>c</sup>	0.5-1

<sup>&</sup>lt;sup>a</sup>Dose that would have a therapeutic effect for 24 hours, according to Summers (8).

receptor method that has been previously described (7, 9).

The total doses of all medications administered to each patient during the 24 hours before the mental status examintion were then used to calculate a drugrisk (for delirium) number according to the method of Summers (8). In this method, drugs that may be associated with production of delirium are assigned to one of three classes (see table 1). Dose level numbers are assigned according to the following criteria: dose level 1 indicates a dose range that would not have a therapeutic effect for a 24-hour period, dose level 2 is a range that would have a therapeutic effect for a 24-hour period, and dose level 3 exceeds that. For each drug administered to a patient in the preceding 24 hours, a drug-risk number is calculated as the product of the class of drug and the dose level. For example, morphine sulfate is a class III drug with a level 2 dose ranging from 25 to 50 mg. Thus, if 70 mg of morphine sulfate were administered in 24 hours, the drug-risk number for this drug would be 9 (III×3). The total drug-risk number for each patient is the sum of the drug-risk numbers of all drugs received. Summers found, in his prospective study (8), that higher total drug-risk numbers were more likely to be associated with development of delirium than were lower ones.

# **RESULTS**

Nine of the 25 patients (36.0%) were clinically diagnosed as delirious. The average age of delirious patients was 60.0 years (range=29-74 years), and that of the nondelirious patients was 57.0 years (range= 29-76 years). The proportions of men were similar for the two groups (77.7% of the delirious patients and 68.8% of the nondelirious group). The mean ±SD level of anticholinergic activity for the delirious patients was 4.67±3.3 ng/ml atropine equivalents, which was significantly higher than that for the nondelirious patients, which was  $0.81\pm1.0$  ng/ml atropine equivalents (t=3.46, df=9, p=.007, Student's t test for unequalvariance, two-tailed). The mean ±SD drug-risk number was higher for delirious patients  $(12.0\pm9.2)$  than for the nondelirious group  $(8.3\pm6.4)$ , but this difference did not attain statistical significance (t=1.1, df=12, p=.3, Student's t test for unequal variance, twotailed).

# **DISCUSSION**

Our study demonstrates that the presence of delirium in critically ill surgical patients is significantly associated with high plasma anticholinergic activity as determined by radioreceptor assay. Delirium tends to be related to the administration of large amounts of medication known to be associated with delirium, as predicted by the drug-risk number.

One advantage of serum or plasma measurements is that the anticholinergic effects of pharmacologically active metabolites as well as combinations of drugs with subtler, heretofore unknown anticholinergic activity can be accounted for. This may explain why there was a stronger relationship of the clinical diagnosis of delirium to anticholinergic levels than to the drug-risk number.

The sample of patients seems to have been representative of patients in the surgical intensive care unit. Mental status examinations were made without prior knowledge of medications received by the patients or of plasma anticholinergic activity. All drug levels were determined after the mental status examination was done. Thus, it appears likely that the associations demonstrated in the study do not reflect observer bias.

It is important to note that it was possible to determine the mental status of all patients in the unit who met the criteria for study. By mental status examination alone, we could define a group of patients who tended to have high plasma anticholinergic activity. Although the etiologies of the delirious states we observed are complex, our data suggest that determinates

bWhen infused as a continuous intravenous "drip," dose was not accurately calculated but, rather, was considered to be at level 2. Drug not listed by Summers (8). Class and level 2 dose decided by the authors on the basis of information in reference 10.

nation of anticholinergic activity may be a useful means of assessing drug intoxication and that the administration of medication with anticholinergic activity may contribute significantly to the pathogenesis of delirium. This study supports the belief that the mental states of patients in critical care units should be monitored carefully and that abnormalities which suggest delirium should lead to a careful review of medications that might be contributing to the delirium. The role of determinations of serum or plasma anticholinergic activity levels merits further consideration.

#### REFERENCES

- Knights EB, Folstein MF: Unsuspected emotional and cognitive disturbance in medical patients. Ann Intern Med 1977; 87:723– 724
- 2. DePaulo JR, Folstein MF: Psychiatric disturbances in neurolog-

- ical patients: detection, recognition, and hospital course. Ann Neurol 1978; 4:225-228
- 3. Folstein MF, Fetting JH, Lobo A, et al: Cognitive assessment of cancer patients. Cancer 1984; 53 (suppl 10):2250-2255
- Rabins PV, Folstein MF: Delirium and dementia: diagnostic criteria and fatality rates. Br J Psychiatry 1982; 140:149–153
- Dubin WR, Field HL, Gastfriend DR: Postcardiotomy delirium: a critical review. J Thorac Cardiovasc Surg 1979; 77:586–594
- 6. Golinger RC: Delirium in surgical patients seen at psychiatric consultation. Surg Gynecol Obstet 1986; 163:104–106
- Tune LE, Holland A, Folstein MF, et al: Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981; 2:651-652
- 8. Summers WK: A clinical method of estimating risk of drug induced delirium. Life Sci 1978; 22:1511–1516
- Tune LE, Coyle JT: Acute extrapyramidal side effects: serum levels of neuroleptics and anticholinergics. Psychopharmacology 1981; 95:9–15
- Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman and Gilman's the Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1985

# Profound Hypoglycemia With the Addition of a Tricyclic Antidepressant to Maintenance Sulfonylurea Therapy

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Cases of profound hypoglycemia after the initiation of tricyclic antidepressant therapy in two patients taking sulfonylureas are described. To the authors' knowledge, this is the first report of a potential drug interaction between tricyclic antidepressants and sulfonylureas.

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S ulfonylureas interact with several classes of drugs, causing alterations in blood glucose levels. Reports of drug interactions involving sulfonylureas and

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psychotropic agents have been limited to monoamine oxidase inhibitors (MAOIs) and dopamine antagonists (1). Reversible glucose intolerance with the dopamine blockers loxapine and amoxapine has been reported (2). Although the mechanism is not known, it has been postulated that dopamine may inhibit insulin secretion. In contrast, hypoglycemia occurs when sulfonylureas are used with an MAOI in diabetic subjects (3, 4). Mechanisms proposed for this interaction include 1) chronic administration of an MAOI, causing tissue depletion of catecholamines and failure of the normal homeostatic compensatory adrenergic response to hypoglycemia, and 2) adrenergic receptor antagonism (1, 3, 4). No significant effect on blood glucose occurs in nondiabetic subjects (3).

To our knowledge, this article is the first to report the occurrence of hypoglycemia in a patient when a tricyclic antidepressant was added to chronic sulfonylurea therapy.

# CASE REPORTS

Case 1. Ms. A, a 71-year-old white woman with type II diabetes mellitus, was started on a regimen of 25 mg/day of doxepin for major depressive disorder. Within 1 week her dose of doxepin was increased to 50 mg/day. Eleven days after starting doxepin she was brought to the emergency room in an unresponsive state. No seizure activity, incontinence, dysphagia, or overdose was reported by her live-in caregiver, nor had she ingested alcohol or drugs known to interact with sulfonylureas.

On admission Ms. A was oriented and afrebile and had normal vital signs. The results of a neurological examination were normal. Levels of electrolytes, WBC, hematocrit, BUN, and serum creatinine level were all within normal limits. Her blood glucose level was 75 mg/dl. Her medications included 1 g/day of tolazamide (with 500 mg taken 12 hours before admission), 75 mg/day of doxepin, digoxin, furosemide, and potassium chloride. Twelve hours after admission, Ms. A was found to be unresponsive, with a blood glucose level of 35 mg/dl. She was given dextrose, fluids, and electrolytes and improved. On her 4th hospital day, tolazamide was restarted at the reduced dose of 100 mg/day. Her fasting blood glucose level at discharge was 163 mg/dl. She continued to take doxepin, 75 mg/day, and tolazamide, 100 mg/day, after discharge and did not experience any further hypoglycemic episodes.

Before her admission, there had been no record of a fasting blood glucose level less than 200 mg/dl for 5 years. Because she had refused insulin, Ms. A had been maintained on 1 g/day of tolazamide, with poor control of blood glucose (i.e., a level of 300–400 mg/dl) since a below-the-knee amputation 6 months before the current admission. Before the amputation she had received 3 g/day of tolbutamide for 3 years, and her blood glucose levels had been in the 300–400 mg/dl range.

Case 2. Ms. B, a 59-year-old white woman, was transferred to the psychiatric ward 24 hours after an overdose of an unknown quantity of benzodiazepines and nonsteroid anti-inflammatory agents. Her medical problems included obesity, hypertension, degenerative joint disease, and type II diabetes mellitus. Before she took the overdose she had been chronically taking hydrochlorothiazide, 25 mg/day, potassium chloride, 20 meq/day, and chlorpropamide, 250 mg/day.

During the observation period her vital signs and electrolyte levels were stable and within normal ranges. Her BUN and serum creatinine levels were 15 mg/dl and 0.7 mg/dl, respectively. An ECG showed normal sinus rhythm with a normal QR interval. Results of drug screens for salicylates, acetaminophen, lithium, and tricyclic antidepressants were all negative. Her blood glucose level ranged from 180 to 218 mg/dl when she was taking 250 mg/day of chlorpropamide.

Nortriptyline was started and titrated to 125 mg/day in 3 days. Four days after the maximum dose of nortriptyline was attained, Ms. B's blood glucose level dropped to 50 mg/dl, requiring administration of glucagon, 1 mg i.m. Because of this hypoglycemic episode, it was decided that the chlorpropamide should be discontinued. During the remainder of her 4-week hospitalization, she continued to take nortriptyline, 125 mg/day, and her blood glucose level was stable at 90–120 mg/dl.

# DISCUSSION

In the first case, the dramatic reduction in blood glucose occurred 11 days after the addition of doxepin to chronic tolazamide therapy. Hypoglycemia secondary to an overdose was unlikely, because the patient had a live-in caregiver who supervised her medication intake, and the quantity of drug remaining in her prescription vials confirmed compliance with her regimen. Other possible explanations for hypoglycemia that were ruled out included recent history of vomiting, decreased food intake, severe intercurrent disease, alcohol ingestion, and ingestion of over-the-counter drugs, i.e., salicylates.

In the second case, hypoglycemia occurred 4 days after nortriptyline was added to chronic chlorpropamide therapy. Because the patient was hospitalized, hypoglycemia was not due to intentional ingestion of medication. Although Ms. B had reduced her food intake secondary to depression, anorexia was present both during the time her blood glucose ranged from 180 to 210 mg/dl and when the hypoglycemic episode occurred. Reduced elimination of the sulfonylurea as a cause for exaggerated hypoglycemic effect is unlikely, because both patients had stable renal and hepatic function on tests before and during hospitalization.

Evidence which supports a probable drug interaction is the fact that the first patient had had stable but elevated blood glucose levels for at least 6 months on a regimen of tolazamide, 1 g/day, before the addition of doxepin. Further, after the acute hypoglycemic episode, when the patient was stable on the doxepin regimen, the effective daily tolazamide dose was 10% of that required before tricyclic antidepressant therapy. In addition, her fasting blood glucose level remained closer to the "normal" range after stabilization on the regimen of doxepin and tolazamide than when she was taking the sulfonylurea alone.

Physicians should be aware that a potential drug interaction exists between sulfonylureas and tricyclic antidepressants. Patients' blood glucose levels should be monitored after the addition of a tricyclic antidepressant to chronic sulfonylurea therapy. Sulfonylurea hypoglycemic agents currently available in the United States include acetazolamide, chlorpropamide, glipizide, glyburide, tolazamide, and tolbutamide.

- 1. Hansen JM, Christensen LK: Drug interactions with oral sulphonylurea hypoglycaemic drugs. Drugs 1977; 13:24–34
- Tollefson G, Lesar T: Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. J Clin Psychiatry 1983; 44:347–348
- Cooper AJ: The action of mebanazine, a monoamine oxidase inhibitor antidepressant drug in diabetes, part II. Int J Neuropsychiatry 1966; 2:342–345
- Mahfouz M, Abdel-Maguid R, El-Dakhakhny M: Potentiation of the hypoglycaemic action of tolbutamide by different drugs. Arzneimittelforschung 1970; 20:210–212

# DSM-III Diagnoses Associated With Dyspepsia of Unknown Cause

Guido Magni, M.D., Francesco di Mario, M.D., Giuseppina Bernasconi, M.D., and Gaetano Mastropaolo, M.D.

The frequencies of DSM-III diagnoses in 30 patients with dyspepsia of unknown origin and 20 patients with organic dyspepsia were compared. Dyspepsia of unknown origin was associated with a higher prevalence of psychiatric diagnoses (86.7% versus 25.0%), particularly anxiety disturbances (66.7%).

(Am J Psychiatry 1987; 144:1222-1223)

D yspepsia is a common symptom (1) and is usually characterized by the presence of pain, nausea, or discomfort that is referred to the upper alimentary tract. Only some of these patients suffer from peptic ulcer disease; the majority are afflicted with nonulcer dyspepsia. This term is applied to a heterogeneous group of patients that encompasses subjects with detectable conditions such as gastroesophageal reflux and irritable bowel syndrome and others in whom no organic pathology responsible for the symptom can be found. The dyspepsia in these cases has been provisionally called "essential" (2).

It has been hypothesized that psychological factors could play a contributory role in essential dyspepsia, leading some authors to define it as "nervous dyspepsia" (1). However, few studies have been carried out to determine whether psychological suffering is present in these subjects. Furthermore, to the best of our knowledge, research on the presence of psychiatric disturbances that uses clear and definite criteria such as those contained in *DSM-III* is lacking. That was the aim of our study.

# **METHOD**

Thirty consecutive outpatients, 15 men and 15 women, with a mean ± SD age of 39 ± 12 years (range=

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20-60 years) were studied. Twenty were married, eight were single, and two were widowed. The educational level was low in most cases; the mean±SD number of years of schooling was 8.5±3.6. All the subjects were seen at the Gastroenterology Unit of Padua University because of essential dyspepsia. In this study the term "dyspepsia" is defined according to the criteria reported by Talley et al. (3), namely, any pain, nausea, or discomfort referred to the upper alimentary tract that 1) is either intermittent or continuous, 2) has been present for 1 month or more, and 3) is not precipitated by exertion and is not relieved within 5 minutes by rest, excluding patients with jaundice, dysphagia, or bleeding.

All the subjects underwent upper panendoscopy, which did not find evidence of acute or chronic peptic ulcer, esophagitis, gastritis, duodenitis, or carcinoma. Patients were excluded if they had a history of peptic ulcer disease, preceding gastric surgery, overwhelming medical illnesses, or clinical evidence of gastroesophageal reflux or irritable bowel syndrome. All underwent ultrasonography or oral cholecystography to rule out the presence of gallstones. They all underwent a semistructured interview with the same psychiatrist that lasted 1½ hours and was largely based on flow sheets from *DSM-III*, although some specific questions concerning dyspepsia were included.

The diagnoses were determined by consensus of the consultant psychiatrist (G.B.) and a senior trainee in psychiatry (G.M.), who were aware of the patients' gastrointestinal diagnoses.

A comparison group of 20 patients, similar to the experimental group in age, sex, marital status, and educational level, underwent the same interview. They were outpatients seen at the Gastroenterology Unit because of nonulcerous dyspepsia of organic nature, i.e., gallstones (N=12) or hiatus hernia (N=8).

All patients agreed to cooperate with the study and gave their informed consent verbally, as is customary in Italy.

# **RESULTS**

The results are presented in table 1. Of the patients with dyspepsia of unknown origin, 26 (86.7%) had

TABLE 1. DSM-III Diagnoses for 30 Patients With Dyspepsia of Unknown Origin and 20 Patients With Organic Dyspepsia

		psia of vn Cause		Organic Dyspepsia	
Diagnosis	N	%	N	%	
Axis I <sup>a</sup>	26	86.7	5	25.0	
Generalized anxiety disorder	16	53.3	3	15.0	
Simple phobia	2	6.7	0	0.0	
Atypical anxiety disorder	2	6.7	1	5.0	
Hypochondriasis	2	6.7	0	0.0	
Adjustment disorder with anxious mood Adjustment disorder with	2	6.7	0	0.0	
mixed emotional features	1	3.3	0	0.0	
Dysthymic disorder	1	3.3	1	5.0	
Axis II—histrionic personality					
disorder	1 <sup>b</sup>	3.3	0	0.0	
No diagnosis	4	13.3	15	75.0	

<sup>&</sup>lt;sup>a</sup>The difference between groups in the frequency of axis I diagnoses was significant ( $\chi^2$ =19, df=1, p<.001).

<sup>b</sup>This patient had also an axis I diagnosis.

one axis I diagnosis, and one also had an axis II diagnosis. The majority of axis I diagnoses were for anxiety disorders. There were few cases of somatoform, affective, or adjustment disorders. No psychotic disorders were found. The only diagnosis on axis II was histrionic personality disorder. Five patients (25.0%) in the comparison group had diagnoses, all on axis I. The difference between the two groups in the frequency of axis I diagnoses was statistically significant.

# DISCUSSION

The group of patients we studied, although not very large, comprised subjects in whom organic causes for dyspepsia had been carefully assessed and excluded. One of the strengths of the study is that the group was, from this point of view, homogeneous.

The presence of psychological suffering in patients with essential dyspepsia has received relatively little investigation. Magni et al. (4) compared the Middlesex Hospital Questionnaire scores of 27 patients with essential dyspepsia and 27 matched neurotic patients. On almost all the subscales of the test no statistical differences emerged between the two groups, confirming the hypothesis that neurotic problems are present in patients with essential dyspepsia.

Talley et al. (3) reported that 76 patients with dyspepsia of unknown cause were more neurotic, anxious, and, to a lesser extent, depressed than healthy control subjects and that their levels of psychological distress were similar to those of duodenal ulcer patients

The studies by Magni et al. and Talley et al. used

only rating scales. Our data were gathered through clinical interviews, and psychiatric diagnoses were made. We found a high prevalence of anxiety disorders in essential dyspepsia and low rates of somatoform and affective disorders. It is difficult to interpret these psychiatric disorders as merely nonspecific responses to discomfort, because the subjects with "organic" dyspepsia showed a much lower rate of psychopathology.

Of course, it is possible that the higher rate of psychiatric diagnoses in these subjects was due to selection—that anxious patients with dyspepsia present themselves for attention while others remain at home. Some weight must be given to that view. However, the high percentage of diagnoses of generalized anxiety disorder is noteworthy, since Barlow et al. (5) recently reported that only a relatively small number (N=12, 11%) of 108 patients assessed in an anxiety disorders clinic received this diagnosis. It is likely that the different frequency in the diagnosis of generalized anxiety disorder is linked to the different samples studied. Anxiety seems to be highly connected not only to essential dyspepsia but also to other pathologies of the alimentary tract, such as peptic ulcer disease (6, 7), gastroduodenitis (6), and irritable bowel syndrome (8).

It is possible that the connection between anxiety and some alimentary tract disturbances could be mediated by the autonomic nervous system; stress and emotional arousal can lead to modification of secretion, motility, and blood flow in the digestive system.

It should be remembered that an association between two disturbances does not necessarily indicate a causal link between them; it is possible that other factors could play a contributory role in dyspepsia of unknown cause.

- 1. Data base on dyspepsia. Br Med J 1978; 1:1163-1164
- Talley NJ, Piper DW: The association between non-ulcer dyspepsia and other gastrointestinal disorders. Scand J Gastroenterol 1985; 20:876–900
- 3. Talley NJ, Fung LH, Gilligan IJ, et al: Association of anxiety, neuroticism, and depression with dyspepsia of unknown cause: a case-control study. Gastroenterology 1986; 90:886–892
- Magni G, Di Mario F, Aggio L, et al: Psychological distress in non-ulcerous dyspepsia (letter). Gastroenterol Clin Biol 1985; 9: 86
- Barlow DH, Blanchard EB, Vermilyea JA, et al: Generalized anxiety and generalized anxiety disorder: description and reconceptualization. Am J Psychiatry 1986; 143:40–44
- Magni G, Salmi A, Paterlini A, et al: Psychological distress in duodenal ulcer and acute gastroduodenitis. Dig Dis Sci 1982; 27: 1081–1084
- Magni G, Di Mario F, Rizzardo R, et al: Personality profiles of patients with duodenal ulcer. Am J Psychiatry 1986; 143:1297– 1300
- 8. Palmer RL, Stonehill E, Crisp AH, et al: Psychological characteristics of patients with the irritable bowel syndrome. Postgrad Med J 1974; 50:416–419

# Treatment of Catatonia With Low-Dose Lorazepam

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The authors describe three patients who each had a catatonic syndrome associated with affective psychosis and who responded dramatically to low doses of lorazepam.

(Am J Psychiatry 1987; 144:1224-1225)

Catatonia is a clinical syndrome that has been associated with affective and schizophrenic illness, neurological disorders, infections, and toxic states (1). In particular, neuroleptic-induced catatonia is an important iatrogenic cause of catatonic symptoms (2, 3).

Sedative agents such as amobarbital sodium (Amytal) have long been known to have a transient ameliorative effect on some catatonic patients, a property that has been useful at times for diagnostic interviews (4). Benzodiazepines have also been reported to be effective in the treatment of catatonia. Several investigators have reported improvement of varying duration in catatonic patients after treatment with diazepam (5) or lorazepam (6, 7).

The following is a report of three patients who each had a catatonic syndrome associated with affective disorder and were successfully treated with lorazepam.

# **CASE REPORTS**

Case 1. Ms. A, a 16-year-old white girl, was admitted to the psychiatric ward of a community hospital with a 2-week history of difficulty concentrating, social withdrawal, sleep disturbance, depressed affect, and mood-congruent delusions. She was treated with perphenazine, 24 mg/day, and desipramine, 150 mg/day. After 5 days she was catatonic—mute, immobile, and incontinent. Her perphenazine dose was increased to 88 mg/day, and treatment with imipramine and lithium was begun. However, her symptoms remained unchanged, and she developed significant extrapyramidal symptoms as well.

On the 25th hospital day Ms. A was transferred to Yale-New Haven Hospital, where all medications were discontinued. Over the next 7 days her extrapyramidal

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symptoms gradually abated, but her catatonic symptoms persisted. One week after her transfer an Amytal interview was conducted. She responded freely during the interview, during which she described preoccupations with guilt, delusions, and suicidal ideation. She was able to eat, speak, and care for herself until the next morning, when the catatonia recurred.

Because of her dramatic response to the Amytal interview, she was given a 2-day trial of oral lorazepam, 1 mg b.i.d. She responded with immediate dramatic improvement; she spoke freely and participated in ward activities. The lorazepam was discontinued, and 24 hours later the catatonia recurred.

At this point Ms. A was started on a dose of oral lorazepam, 1 mg b.i.d. On this regimen she improved as before, and after 1 week her delusions were no longer present. Since it was felt that this syndrome might represent the initial presentation of bipolar disorder, lithium carbonate was added. After 3 weeks the lorazepam was gradually discontinued, and after 6 weeks Ms. A was discharged to outpatient care. After 1 month of outpatient treatment she stopped taking lithium and shortly thereafter ended treatment. At 1-year follow-up she was doing well, both socially and at school. She was given a DSM-III diagnosis of major affective disorder with mood-congruent psychotic features.

Case 2. Ms. B, a 20-year-old single white woman, was transferred from a community hospital to a long-term psychiatric hospital for continued treatment of psychotic depression. Her first psychotic episode occurred at age 17 and was diagnosed as mania with mood-congruent hallucinations and delusions. At that time she responded to a regimen of lithium and perphenazine. Subsequently, two additional brief hospital stays were required, one for acute mania and the other for a depressive episode.

The current, fourth hospitalization was characterized by only a partial response to lithium and a series of neuroleptic trials. After Ms. B had been in the hospital 4 months her condition deteriorated further, and her delusions, mutism, and hypersomnia increased. All medications were discontinued, and she gradually became catatonic. After 3 drug-free weeks, during which her condition remained unchanged, lorazepam treatment was begun at a dose of 3.0 mg/day. Seventy-two hours after the first dose of lorazepam, Ms. B began to speak; she requested food and assistance with her hygiene. She also began to walk about freely without evidence of rigidity or posturing. Lithium was then added to the lorazepam regimen.

Over the next 4 weeks Ms. B continued to make steady progress. Her thought disorder and delusions cleared. Eight weeks after beginning lorazepam treatment she was discharged to her home. Lorazepam treatment was discontinued 3 months after discharge, and she was maintained on lithium. At her 4-month follow-up she was stable and was

seeking full-time employment. Her DSM-III diagnosis was bipolar disorder, depressed, with mood-congruent psychotic features.

Case 3. Ms. C, a 38-year-old single Oriental woman, had been hospitalized twice previously for psychotic depression. During her first hospitalization she was treated with imipramine, 150 mg/day, and trifluoperazine, 15 mg/day. Two years later these medications were discontinued, and she became symptomatic within a week. She was rehospitalized for 4 months and improved gradually on a regimen of imipramine, 150 mg/day, and trifluoperazine, 25 mg/day.

The next year the trifluoperazine dose was gradually reduced to 10 mg/day. Ms. C's symptoms of psychotic depression soon recurred, and at the time of her third admission she was nearly mute and had preoccupations with guilt and nihilistic delusions. She was treated with perphenazine, 32 mg/day, but did not improve. By the 7th hospital day she was catatonic; she appeared somewhat stiff and had minimal cogwheeling but was without waxy flexibility or rigidity.

At this point lorazepam was administered. After receiving 2 mg of lorazepam over 18 hours, she got out of bed on her own, requested a meal, and began talking spontaneously. She was placed on a regimen of lorazepam, 3 mg/day, perphenazine, 32 mg/day, and imipramine, 150 mg/day. Over the next 3 days she was more spontaneous, her somatic delusions cleared, and she was able to talk about her religious delusions.

Because of her continued complaints about sedation, lorazepam was discontinued. After 48 hours she was again catatonic. Lorazepam, 4 mg/day, was reinstituted, and within 12 hours Ms. C was talking, going to therapy groups, and attending to her hygiene and nutrition.

Her improvement continued over the next 3 weeks with a regimen of imipramine, 75 mg/day, perphenazine, 16 mg/day, and lorazepam, 4 mg/day. Ms. C was able to return to work after discharge, although her chronic religious delusions, which had been present intermittently since her first episode 3 years earlier, still remained. Her DSM-III diagnosis was major affective disorder with mood-incongruent psychotic features.

# **DISCUSSION**

The cases of catatonia presented here each showed dramatic improvement with lorazepam. In the first case lorazepam was administered 1 week after discontinuation of neuroleptics and in the second case after 3 weeks. Although neuroleptic catatonia cannot be excluded, it seems likely that the catatonia in these two cases was part of a psychopathological syndrome.

In the third case the patient was receiving perphenazine, so neuroleptic catatonia may have played some role, although she had previously received higher neuroleptic doses without developing catatonic symptoms. The favorable response to lithium maintenance after lorazepam treatment in two of the cases suggests a specific nonneuroleptic pharmacologic regimen for cases of catatonia that may be manifestations of bipolar disorder. Such individuals may be unusually sensitive to acute and long-term side effects of neuroleptics, so definitive treatment without neuroleptics may have important advantages (8).

Lorazepam and barbiturates may act by means of similar mechanisms in catatonia, although subacute treatment of catatonia with benzodiazepines is likely to be more feasible because of the minimal sedation with the doses used in our cases. Benzodiazepines have been used increasingly as adjunctive agents in the management of psychotic agitation, usually at doses considerably higher than those employed in the present cases (9, 10). However, our cases and others (5–7) indicate that benzodiazepines may have a primary role to play in a major psychiatric disorder other than the panic and anxiety syndromes—namely, catatonia.

- 1. Gelenberg AJ: The catatonic syndrome. Lancet 1976; 1:1339-
- 2. Gelenberg AJ, Mandel MR: Catatonic reactions to high-potency neuroleptic drugs. Arch Gen Psychiatry 1977; 34:947-
- 3. Fricchione GL: Neuroleptic catatonia and its relationship to psychogenic catatonia. Biol Psychiatry 1985; 20:304-313
- 4. Perry JC, Jacobs D: Overview: clinical applications of the Amytal interview in psychiatric emergency settings. Am J Psychiatry 1982; 139:552-559
- 5. McEvoy JP, Lohr JB: Diazepam for catatonia. Am J Psychiatry 1984; 141:284-285
- 6. Walter-Ryan WG: Treatment for catatonic symptoms with intramuscular lorazepam. J Clin Psychopharmacol 1985; 5: 123-124
- 7. Heuser I, Benkert O: Lorazepam for a short-term alleviation of mutism (letter). J Clin Psychopharmacol 1986; 6:62
- 8. Bowers MB: Cerebrospinal fluid homovanillic acid and hypokinetic side effects of neuroleptics. Psychopharmacology (Berlin) 1985; 85:184-186
- 9. Wolkowitz OM, Pickar D, Doran AR, et al: Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. Am J Psychiatry 1986; 143:85-87
- 10. Csernansky JG, Lombrozo L, Gulevich GD, et al: Treatment of negative schizophrenic symptoms with alprazolam: a preliminary open-label study. J Clin Psychopharmacol 1984; 4:349-

# Book Forum

# Nancy C. Andreasen, M.D., Ph.D., Editor

# **PSYCHODYNAMICS**

The Psychology of Men: New Psychoanalytic Perspectives, edited by Gerald I. Fogel, Frederick M. Lane, and Robert S. Liebert. New York, Basic Books, 1986, 299 pp., \$26.95.

Freud's conceptualization of male psychosexual development is among the most clearly articulated and enduring elements of classic psychoanalytic theory, with an elegant four-step simplicity: phallic exploration, oedipal conflict, castration anxiety, and resolution by means of identification. But this very simplicity has, in times past, served a formulaic dogmatism that saw unresolved oedipal wishes lurking in every assertive act and castration anxiety in every retreat. The Psychology of Men reflects a maturing perspective in which the art and science of interpretation have become more real as the theory has expanded to handle more complexity. In this collection of papers literature, sociology, and history join clinical observations drawn from a wide diversity of sources to achieve a new integration of multiple points of view. Given the scope and complexity of the subject matter, it is unreasonable to expect more than a progress report, and this one is encouraging.

Two themes recur throughout the book to modify and extend Freud's original theories of male psychology. Important as it is, there is far more to becoming a man than having, using, and safeguarding one's penis. In these papers men are seen to love, envy, fear, and identify with mothers and sisters as well as with fathers and brothers. Thus, male development and psychology can no longer be seen, as they have been, primarily in phallocentric terms. The second focus of this book is bisexuality; although Freud took bisexuality into account, that topic is vastly expanded here. In addition to a man's encounter with his own femininity a different issue is added—his encounter with women. George Stade, Professor of English and Literature at Columbia University and author of the first chapter in the book, is cited by Arnold Cooper in the following evocative summary: "All men have spent a significant formative part of their lives totally in the care of women who wiped their bottoms, fed their mouths and their egos, and held their hands whenever there was danger or difficulty. The prevalence of forms of macho behavior can generally be understood as counteracting the inner fear of reversion to this earlier state" (p. 113).

In his own chapter, Professor Stade writes an erudite and

In his own chapter, Professor Stade writes an erudite and immensely playful thesis on male psychology as revealed in the literary classic *Dracula*, by Bram Stoker. He reasons that men reveal what ails them in what they say about women, and the enduring popularity of *Dracula* establishes its credentials in this regard. All but one of Dracula's victims are women, and the single male victim is an effeminate madman. Dracula's gaunt, hypnotic, wolf-like demeanor attracts virginal, defenseless damsels who sleepwalk toward his serpentine bite into submission. Female sexuality, aroused, is insatiable and selfish and must be destroyed, as it is in the orgasm of vampiric death. Fears of nymphomania abound, and the duty of good men and women is to extinguish this

vile fire. The bisexuality inherent in Dracula's character must be suppressed as well, and in this regard it is noteworthy that vampires are ageless.

John Munder Ross reviews and updates the stages of a man's psychosexual development, with an emphasis on those female components which are essential to masculine identity. It is a peace which must be made and against which many forms of hypermasculinity defend. Ross elaborates on Lawrence Kubie's idea that there exists in everyone a drive to become both sexes. Everyone suffers "something" envy. Ross suggests a line of development in which the boy must first "disidentify with mother" in order to proceed toward male sexuality and fatherhood. The pull of feminine components is a persistent threat to this movement, and one for which society offers scant opportunity for sublimation and integration before the achievement of marriage and fatherhood. The theme of hidden, conflicted feminine components in male character are further elaborated in chapters by Ethel Person and Roy Schafer. Person uses the fantasy of the omniavailable woman to suggest a universal fear of genital inadequacy in each boy's oedipal dilemma. She argues that a common transient transvestic oedipal solution is but one reflection of the vicissitudes of male bisexual concerns, fantasies, and conflicts.

Roy Schafer carries the reader on a different vector in his reflections on men's struggle against sentimentality. He reviews his own earlier concerns with language, bringing sentimentality together with other "key words," such as genuineness, individuality, freedom, and integrity, and he describes them as "strands in a web of significance" (p. 96). Such key words are essential tethers for understanding complex behavior, and they form a texture of understanding quite different from the dense metaphor of the psychosexual stages of development. Mostly, men who struggle against sentimentality are expressing the need to renounce some aspect of bisexuality once suffered or dangerously enjoyed. But there are myriad meanings and possibilities, and the word "sentimentality" serves to organize the clinical exploration into a focus of actions and meanings.

In an important contribution, Arnold Cooper reexamines the concept of castration anxiety within the larger context of human fears. He prefers to call them "terrors," reminding us that all men fear some things and some men fear everything. Human development proceeds through a forest of terrors, from bodily integrity though separation-individuation, preoedipal aggressions of orality and anality, and, finally, given optimum conditions, oedipal conflicts, where conventional castration anxiety emerges. He offers case material to demonstrate the complex layering of oedipal and preoedipal issues, anchored on the important truth that defenses against fears may themselves be fears at a higher level of organization. "Castration anxiety [is] so close to consciousness ... because it is . . . the least feared of the baby fears, representing the compromise formations arising out of earlier fears and hiding within it the earlier fears, which are far more threatening.... Castration anxiety is often a desperate attempt to 'escape forward' ... to more advanced levels of

representation, escaping from the more primitive and frightening versions of narcissistic threat" (pp. 118–119). Defenses against the disorganizing qualities of primitive fears achieve secondary autonomy and are experienced as powerful wishes of the highest priority, holding the deeper fears safely remote from consciousness. This revision of theory is of major importance and has far-reaching consequences in our clinical work.

Frederick Lane presents the case of a man in whom a fantasied vulva was central. This man's gender identity was unambiguously male, but he had a powerful envy of female prerogatives to be passive, exempt from pressures to achieve, and protected from the aggression of others. These wishes emerged in his analysis as more prominent determinants of behavior than libidinal wishes for a female sexual experience. In this connection one is reminded of the protagonist psychoanalyst in Janet Malcolm's book Psychoanalysis: The Impossible Profession (1), who confessed to her that his deepest wish was to be a beautiful woman. This leads to Otto Kernberg's chapter, in which he discusses male perversions. He reviews normal polymorphous perverse behavior in order to show the vastly different structure of homosexual behavior in normal and neurotic as compared with borderline and narcissistic disorders. In the end, however, he reverts to phenomenology to support the classic psychoanalytic conclusion: "We just do not find, except very rarely, male homosexuality without significant character pathology" (p. 175). Robert Liebert's chapter reviews male homosexuality from a historical perspective-from ancient Greece through the Renaissance, a condensed survey of 2,000 years. Three conclusions emerge: 1) social forms influence conflict resolution by defining acceptable confines of behavior, 2) Freud's general postulates about bisexuality are strongly supported, and 3) despite wide ranges in degrees of tolerance for sexually deviant behavior, an "iron law of history" dictates that males must ultimately conform to male gender roles.

Peter Neubauer presents data drawn from observations of fathers providing child care. His work strongly supports the views of others in this book that men's characters are powerfully enriched when their feminine components can be adaptively synthesized into their lives. He finds a useful "regression under the auspices of caring" that allows these fathers to rework some of their own preoedipal aspirations and conflicts. Eugene Mahon reviews adolescent male psychology and finds a rich point of reference in several historical biographies that supplement clinical excerpts to demonstrate ways in which this period of "psychosocial moratorium" serves to reintegrate diverse instinctual and defensive

The final three chapters are on therapy. Donald Meyers and Arthur Schore discuss many of the transferencecountertransference issues that arise when men treat men: Helen Meyers explores the same questions when the therapist is of the opposite sex. Whereas everyone agrees that the gender of the therapist should not be a determining issue, it often is. These discussions usefully highlight many of the hidden traps and snags in treatment. In the final chapter Richard Isay argues against the intrusion of motivation by the therapist to change the sexual orientation of a homosexual patient. The very word "perversion" reflects a moralism in psychoanalytic theory. Isay believes that many therapists unwittingly carry a value-laden orientation which leads them away from a position of neutrality to the improper one of moral arbiter—even in statements as carefully articulated as Kernberg's earlier in this volume. And so this excellent book concludes with a thoughtful discussion of a contemporary

sociopolitical controversy, viewed through a psychoanalytic lens. Such is the scope of this collection.

All three editors and 12 of the 15 contributors to *The Psychology of Men* are affiliated with the Columbia Psychoanalytic Center in New York City. They speak with admirable erudition, achieve a choral balance that is rare in a multiauthored work, and eloquently reaffirm the relevance and vitality of contemporary psychoanalytic theory.

#### REFERENCE

 Malcolm J: Psychoanalysis: The Impossible Profession. New York, Alfred A Knopf, 1981

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Kohut's Legacy: Contributions to Self Psychology, edited by Paul E. Stepansky and Arnold Goldberg. Hillsdale, N.J., Analytic Press (Lawrence Erlbaum Associates, distributor), 1984, 252 pp., \$27.50.

For only in the half-destroyed do we understand the blue that covers the inside of rooms, like doctors who learn by bodies gaping in front of them. But we will never know how blood behaves when it's inside, within the whole body, when the heart shines into it, from far away, in its dark path. (1)

Heinz Kohut devoted the last 15 years of his life to the study of narcissistic character disorders and other preoedipal primary disturbances of the self. One aspect of Kohut's youth that stimulated his sensitivity to the motif of self-fragmentation was the monumental disruption caused by Nazi Germany's Anschluss of Austria, which forced him to abandon his home, the country of his birth, and his way of life in Vienna (2). Although he did not know Freud personally, he went to watch Sigmund Freud leave Vienna on the Orient Express bound for Paris on June 4, 1938. When Freud, unhappy and mortally ill at 82 years of age, looked out the window, Kohut tipped his hat; Freud tipped his hat in return (3). Describing this scene, Kohut said, "I had the feeling of a crumbling universe"; the departure of Freud signified the loss of "everything that I had lived for" (2).

The Nazis threated Kohut as well. Because his father was of Jewish descent, Kohut fled to England and, from there, to the United States:

I was passionately involved with German and Austrian culture. This was the peak of humanity to me—Goethe and the great German philosophers and writers and musicians. I was sitting up in coffeehouses until 3 o'clock in the morning, discussing each night another sonnet of Rilke. You know, this was life for me. And then, all of a sudden, these bullies came along who claimed they were the real Germans and I was all of a sudden a foreigner and didn't belong. It was the end of the world, it was the end of an era. And I had the feeling that it was also the end of my life, in terms of the continuity of my cultural existence. . . . I have led two totally different, perhaps unbridgeable lives. (2)

Kohut's contributions have been uncommonly creative and influential. I expected that *Kohut's Legacy* would offer an expert summary of his theories of the psychology of the self and a perspective on their clinical application to the treatment of narcissism. That the editors of *Kohut's Legacy* were also the editors of Kohut's last and posthumous volume (4) only heightened my expectations.

Kohut's Legacy is a disappointment. The title is misleading because, in fact, Kohut's Legacy is not the legacy of Kohut at all but a collection of papers presented at the fourth Berkeley Self Psychology Conference (1981) and the fifth Atlanta Self Psychology Conference (1982), respectively. The Berkeley Conference was the last one Kohut attended; he died 4 days after it closed. The preface to Kohut's Legacy states that these papers were assembled "by way of exemplifying the enriching legacy of Heinz Kohut." However, in fairness to all, including the contributors, the title of a scholarly work needs to be squarely informative about subject matter. Kohut's Legacy is not.

The editors have endeavored to integrate the theoretical, clinical, and research contributions in this book under the common theme of self and "selfobject." This attempt at unification is not particularly successful because the papers

are quite disparate and far-ranging.

Theoretical papers discuss psychoanalytic history (Basch), "selfobject" transference (Basch and Stolorow), the feminine self (Lang), and shame (Morrison). Clinical contributions take up the treatment of borderline patients (Brandchaft, Stolorow, Adler, and Paul Tolpin), treatment disruptions (Wolf), "selfobjects" and psychotherapy (Basch), and psychoanalytic psychotherapy (Anna Ornstein and Lachmann). Articles on research applications are concerned with children with learning disabilities (Estelle Shane), small group theory (Lofgren), the case of Othello (Muslin), and creativity (Schlesinger).

By and large, Kohut's Legacy is not as original and stimulating as the previous volume of this series, which summarized the proceedings of the third Boston Self Psychology Conference (1980) (5). Several contributions, however, are notable exceptions to this general impression.

Gerald Adler's discussion of the treatment of borderline patients from a self psychological point of view is both important and excellent. Adler's juxtaposition of the different frameworks used by Kernberg and Kohut to understand countertransference experiences draws parallels and builds clinical bridges, a rare phenomenon, between self psychological and object relational points of view. Adler emphasizes that "experiences of aloneness, accompanied by panic, are unique to borderline patients, and are manifestations of specific defects which differentiate them from those patients with narcissistic personality disorders" (p. 120). I am not sure I can agree with that statement. Like Kernberg, Adler draws attention to the borderline individual's chronic sense of emptiness and anger and the primitive, punitive nature of the borderline superego. Using the schema of self psychology, Adler sees all of this resulting from a failure to form "stable holding introjects" (p. 123), but Kernberg (6), from the vantage point of his dyadic object relations theory, considered these manifestations the consequence of a failure

and identity diffusion.

Adler's paper is a welcome counterpoint to Bernard Brandchaft and Robert Stolorow's thesis, promulgated in Kohut's Legacy as well as in a previous paper (7), that "the concept of a borderline personality organization is, largely if not entirely, an iatrogenic myth" (p. 367) and "is symptomatic of the difficulty therapists and analysts have in comprehending the archaic intersubjective contexts in which

to integrate contradictory "good" and "bad" internalized object relationship units, lack of emotional object constancy,

borderline pathology arises" (p. 99). Brandchaft and Stolorow believe that therapists of "so-called" borderline patients habitually fail to grasp their patients' primitive longings and then fail to acknowledge their own lack of understanding. Such repeated empathic failures "in an intersubjective field—a field consisting of a precarious, vulnerable self and a failing, archaic selfobject" (p. 98)—form, in their view, the conceptual basis of borderline personality organization.

Space does not permit here a full refutation of these challenging formulations. I could hardly improve, in any event, on Adler's detailed discussion of the subject (8). Suffice it to say that Kernberg's concept, challenged by Brandchaft and Stolorow, of an intermediate form of psychopathology-a category called borderline personality organizationdescribing level of function in a broad heterogeneous spectrum of severe personality disorders, is most helpful in clarifying diagnostic understanding and treatment planning for many fragile individuals. It alerts the therapist to characteristic and expectable transference and countertransference developments in the course of treatment. Kernberg classified many narcissists as having borderline personality organization, but Adler postulates a "borderline-narcissistic personality disorder continuum . . . with a distinct diagnostic category at each end of the continuum" (p. 119). Brandchaft and Stolorow's discussion may be valid for some selected individuals who suffer from a misdiagnosed narcissistic personality disorder but are able to tolerate the analytic situation. The reminder of the role therapists can play in codetermining such patients' difficulties through empathic failures is helpful indeed. However, Brandchaft and Stolorow's sweeping conclusions are unwarranted for the majority of adults and children with borderline personality organization whose psychopathology can be codetermined at times even biologically because of genetic, congenital, or acquired features. Such individuals are not in psychoanalysis, and only very few could tolerate it—unlike the three analytic patients whose diagnostically incomplete and unsatisfactory anecdotal case material Brandchaft and Stolorow cite to buttress their position.

In two separate articles, Anna Ornstein and Ernest Wolf offer sensitive examples of the creative contribution the psychoanalytic self psychological approach can make to the problem of interpretation. Ornstein's and Wolf's understanding focuses primarily on the structural integrity, the cohesiveness, of the self. Ornstein says, "Any explanation offered to the patient in relation to a single fantasy or dream or symptom ... would not facilitate the evolution of a therapeutic process. Indeed, the opposite would be true: The 'dynamic explanations' of the fantasy, dream, or symptom would fragment the therapeutic experience and carry the treatment into experience-distant terrains" (p. 173).

Finally, Kurt Schlesinger provides a gripping account of artistic achievement as an example of the creative process, the ongoing lifelong activity of the development and renewal of the self. It is a fascinating article and, although I got to it at 2:00 a.m., I could not put down *Kohut's Legacy* until I

had finished reading Schlesinger's paper.

In summary, then, Kohut's Legacy is not an introduction to or an overview of Kohut's carefully wrought theories. One has to turn to the writings themselves (4, 9, 10) to discover his work as a whole. Nevertheless, the lucidity and sophistication of Gerald Adler, Anna Ornstein, Ernest Wolf, and Kurt Schlesinger make the reading of Kohut's Legacy a worthwhile experience. Their papers are sensible and sensitive contributions.

### REFERENCES

- Amichai Y: Elegy on an abandoned village, in The Selected Poetry of Yehuda Amichai. Edited and translated by Bloch C, Mitchell S. New York, Harper & Row, 1986
- Quinn S: Oedipus vs Narcissus. New York Times Magazine, Nov 9, 1980, pp 120–131
- Strozier CB: Glimpses of a life: Heinz Kohut (1913–1981), in Progress in Self Psychology, vol 1. Edited by Goldberg A. New York, Guilford Press, 1985
- 4. Kohut H: How Does Analysis Cure? Edited by Goldberg A, Stepansky P. Chicago, University of Chicago Press, 1984
- Lichtenberg JD, Kaplan S (eds): Reflections on Self Psychology. Hillsdale, NJ, Analytic Press, 1983
- Kernberg OF: Severe Personality Disorders: Psychotherapeutic Strategies. New Haven, Yale University Press, 1984, pp 12–13
- Brandchaft B, Stolorow RD: The borderline concept: pathological character or iatrogenic myth? in Empathy II. Edited by Lichtenberg J, Bornstein M, Silver D. Hillsdale, NJ, Analytic Press, 1984
- 8. Adler G: Discussion of "the borderline concept: pathological character or iatrogenic myth?" by Brandchaft B, Stolorow RD. Ibid
- 9. Kohut H: The Restoration of the Self. New York, International Universities Press, 1977
- Kohut H: The two analyses of Mr Z. Int J Psychoanal 1979;
   60:3-27

ROBERT STERN, M.D., PH.D. New Haven, Conn.

Conceptual Issues in Psychoanalysis: Essays in History and Method, by John E. Gedo. Hillsdale, N.J., Analytic Press (Lawrence Erlbaum Associates, distributor), 1986, 243 pp., \$29.95.

John Gedo notes that historical and methodological studies in psychoanalysis daunt even the scholarly psychoanalyst because he or she lacks the skills of the intellectual historian and the epistemologist. Encouraged by invitations to assess important historical and current developments in psychoanalysis, Gedo has prepared a volume of historical and methodological essays concerning areas that have interested him during a quarter century of highly productive psychoanalytic writing and clinical work. Gedo is optimistic about the therapeutic power of psychoanalysis. He has published in this journal (1) and elsewhere (2) reports summarizing his generally successful and extensive clinical experience. He has systematically described technical innovations (3, 4) that have contributed to that optimism. Now he turns to conceptual issues.

Gedo believes that the contemporary technical armamentarium offers far more than was available to the psychoanalytic practitioner a generation ago. He notes that new findings in psychoanalysis often lead to a typical four-step pattern, however. First, a set of clinical observations is forwarded as a neglected area of clinical theory. Then, cases where the novel observations are salient are defined as a new nosological entity hitherto overlooked. Third, the mode of functioning is detected in increasingly wider circles of patients. Finally, the patterns lose their relevance for differential diagnosis and become the center of a new theoretical framework. Partly to forestall such polarization, Gedo, together with Arnold Goldberg (5), developed a framework for clinical theory broad enough to accommodate analysts of varied persuasions. Despite wide acceptance, however, it did little to avoid the emergence of Kohut's self psychology as an alternative body of clinical theory to mainstream psychoanalysis. The dissidence of Heinz Kohut is indeed discussed in the central two chapters of this book and permeates much of the rest.

The other chapters in the first historical section begin with several recent biographical theses about Sigmund Freud's character and the different proposed effects it had on his work. Gedo takes issue with Sulloway, Masson, and Swales. He then discusses Ferenczi, whom he considers the first true psychoanalytic dissident because he largely adhered to prevailing psychoanalytic observations and theories, in contrast to Jung and Adler, who explicitly disavowed Freudian premises. Ferenczi stressed the pathogenic aspect of parental failures and proposed an active technique that is not authoritarian but supportive, patient, and aimed at mourning the missed gratification of childhood. Many modern psychoanalytically informed therapists of patients with severe personality disorders take a similar stance.

Lou Andreas-Salomé was considered the most distinguished woman in central Europe at the time she joined the psychoanalytic movement in 1912. In fact, she was far better known than Freud himself. Salomé's skepticism and reservations about Freud's drive theory were largely limited to her personal journal and correspondence with Freud, the study of which serves as the foundation of another chapter in the historical section. Gedo devotes a historical chapter to the strictest critic of metapsychology of the next generation, David Rapaport. He notes Rapaport's concern about its lack of systematization and some of the inconsistencies that Kohut later attempted to address with his reworking of the concept of narcissism. Melanie Klein is the dissident who has had most influence worldwide, and Gedo well captures the essence of her theory and technique. Like the chapter on Rapaport, the chapter on Klein is a comprehensive yet brief introduction to its subject.

Chapters seven and eight, on Heinz Kohut, are written from the perspective of one of his closest former collaborators. Gedo notes that efforts to explore the role of preoedipal issues in pathogenesis do not necessitate either dissidence or a total break with established theory. Kohut, however, who began his work as an extension of Hartman's metapsychology, claimed by 1977 that the transferences encountered in psychoanalysis are the patient's reactivated efforts to form a cohesive self. He saw the empathic responses of the analyst as necessary because of failed parental efforts. The Oedipus complex becomes a pathological variant rather than a developmental norm; the analyst becomes a "selfobject" rather than a facilitator of insight; and, in Gedo's view, Kohut at his death was on the verge of becoming the head of an independent movement like those of Adler and Jung.

In the next section, Gedo takes up the methodological difficulties inherent in correlating the direct observation of young children with psychoanalytic theory and technique. He sees a formidable problem in translating the manifest behaviors of preverbal children into a psychology of motivations. In reviewing Henri Parens's work on the development of aggression in early childhood, Gedo is bothered by Parens's disregard for alternatives to drive theory and his imputing subjective motives to an organism whose behavior is not yet under cortical regulation. Gedo's own conception of drive is that "an automatic, preprogrammed action pattern is brought into operation" (p. 154)—admittedly a definition at considerable variance from traditional psychoanalytic usage. To Gedo, rage never arises spontaneously but is always a response to specific circumstances.

Gedo also reviews Joseph Lichtenberg's study of psychoanalysis and infant research, which he feels comes closest to his own views, particularly Gedo's own important concept of the compulsion to unconsciously repeat archaic behavior patterns that are without symbolic representation. Gedo stresses the necessity of helping all patients deal with the pathogenic legacies of their personal presymbolic era by teaching them to counter stimulus overload and to symbolically encode primary body experiences so that they are assimilated into the individual's set of acknowledged personal aims. If this is properly done, Gedo believes the patient will have no lifelong need for a "selfobject," as Kohut claimed. To Gedo, "selfobjects" are necessary only when there has been inadequate reconstruction of the exact nature of the early experiences being echoed in the analysis. Without it, the patient cannot be taught the psychological skills necessary to handle life on his or her own.

Gedo's aim is to show that in cases of irreconcilable controversy, nobody had a monopoly on truth, because while firm data about preverbal mental life were lacking, everyone was forced to base theory on guesswork. John Gedo's style is a rarity—a delightful mixture of affective personal response and erudition that enlivens psychoanalytic history and refreshes the reader.

### REFERENCES

- Gedo JE: A psychoanalyst reports at mid-career. Am J Psychiatry 1979; 136:646-649
- Gedo JE: Psychoanalysis and Its Discontents. New York, Guilford Press, 1984
- Gedo JE: Beyond Interpretation. New York, International Universities Press, 1979
- Gedo JE: Advances in Clinical Psychoanalysis. New York, International Universities Press, 1981
- Gedo JE, Goldberg A: Models of the Mind. Chicago, University of Chicago Press, 1973

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Moses: A Psychodynamic Study, by Dorothy E. Zeligs, Ed.D. New York, Human Sciences Press, 1986, 442 pp., \$39.95.

Zeligs ambitiously attempts to understand the needs of the ancient Hebrews by examining the recorded life of Moses, as revealed in the first five books of the Bible, the Pentateuch. Her basic assumption is that the Biblical stories are narrated from the viewpoint of the hero and reflect his unconscious fantasies. These tales can then be adopted by the group whose thoughts and wishes they express; Moses becomes the collective ego of the group, and his life is seen as "synonymous with the development of the superego of the group" (p. 45).

What Zeligs finds in the Pentateuch is a developmental view of Moses's relationship with God, a record of his lifelong quest for greater intimacy with God, and the conflicting fear of such closeness with its attendant danger in the loss of self-identity. By applying psychoanalytic concepts and techniques to the life of Moses, Zeligs attempts resolution of previously obscure references and apparently unrelated incidents, as well as the disclosure of hidden motives. Her analysis reveals that problems in the text occurred most often "where the content dealt with forbidden aspects associated with the oedipal situation, such as sexuality in relation to incestuous objects and rivalry between fathers and sons" (p.

21). Through examination of the defense mechanisms used by Moses, whose story is held to be created by individuals revealing their own defenses and difficulties, Zeligs contends that the "Hebrews, over a long period of time, evolved a form of sublimation, a working through of the conflict, which led to new paths in the fields of morality and religion" (p. 417). Moses's life story reflects his struggles and aspirations as well as those of the group: "In the mass oedipal involvement that the Bible expresses, the feelings for the mother were sublimated in a love for the land, which became the good mother . . . and in an acceptance of the Torah, or religious law, the words of the father" (p. 419).

To be sure, Zeligs's task by its very nature leads her into a morass. A psychological profile of a person who has been dead for some 2,000 years is tentative at best. To then abstract from that profile the motivations and aspirations of an entire race of people is yet another tenuous leap. Still, Zeligs manages her task admirably, trying to avoid the trap of overdeterminism, although this sometimes leads to commentary containing little firm ground to build on. In a not uncommon paragraph, all three sentences are qualified: "It is also possible . . . . In that event we can assume . . . . Under any circumstances, however, it seems ..." (p. 37). The following paragraph begins, "When analyzed thus, in the light of objective reality...." This is a very tentative "objective reality." In short, there is a great deal that Zeligs fills in with hypotheses which seem solid, workable, and logical but which finally have to be savored with a large grain of salt. Perhaps to keep this palatable, she liberally sprinkles the text with quotes from other authorities. However, this tendency toward an overreliance on other critics sometimes draws attention away from Zeligs's own thesis; she pushes too hard to have her case accepted.

Those interested in the social and cultural background of the Jews or in the application of psychoanalysis outside a therapeutic setting will want to read this book. What Zeligs attempts is intellectually engaging; however, more emphasis on the connection between teller and tale—which she apparently wishes to make—would have strengthened her study.

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### **STRESS**

Stress Response Syndromes, 2nd ed., by Mardi Jon Horowitz, M.D. New York, Jason Aronson, 1986, 346 pp., \$35.00.

The dilemma of revising a book such as Stress Response Syndromes is similar to the one faced by Coca-Cola in revising the recipe for Coke. It is hard to improve on a product that has become a classic. Unlike the travails of the soft drink, the new version of this book is a winner, while the first edition will remain a classic.

Since the book was first published in 1978 there has been a multitude of changes in mental health research and practice. Many of these changes emerged directly or indirectly due to the work of Mardi Horowitz and his colleagues, particularly the formulations described in *Stress Response Syndromes*. In 1980 APA published *DSM-III*. For the first time this manual included the diagnosis of posttraumatic stress disorder. As those familiar with the work of Horowitz know, posttraumatic stress disorder is a diagnosis that linked together a wide variety of disorders and syndromes exclu-

sively associated with specific types of highly stressful events: war and concentration camp imprisonment, war combat, terrorist attacks and imprisonment, man-made and natural disasters, fires, major accidents, rape, and other violent crimes.

Posttraumatic stress disorder has become, for better or worse, one of the most important new diagnostic categories in psychiatry. Not only has it changed mental health research and treatment—both public and private—it has affected the judicial system in terms of both insanity defense and tort case methods. Most who were involved in the development of this new diagnosis acknowledge that Stress Response Syndromes played a key role.

Mardi Horowitz and his colleagues have successfully revised this classic text. Much to his credit he decided to retain the essential descriptions of stress response syndromes, though some of the rich historical descriptions were dropped. Generally, he chose to expand and revise the chapters and sections focusing on diagnosis, theory, and treatments. For example, the new chapter on theory incorporates the more recent research on human psychological response to stress. The diagrams of his theoretical formulations are greatly improved now and complement this nicely written book, although it is still encumbered at times with unnecessary jargon.

Perhaps the most controversial addition is the discussion of posttraumatic stress disorder. Here he points out that the diagnostic criteria for posttraumatic stress disorder in *DSM-III*, which define what constitutes a traumatic event, may be too narrow. He notes that some highly stressful events are not necessarily "outside the range of human experience," as specified by the manual, "but are shocking and uncommon experiences for the individual who undergoes them for the first time" (p. 32). This is consistent with the revised version of *DSM-III* (*DSM-III-R*), published this year.

Horowitz also points out that intrusive thoughts and feelings which may characterize a stress-induced disorder are not unique to posttraumatic stress disorder. He notes that they are simply "a sign of strain to psychological systems in general and may occur in a variety of disorders, following internal stressful events such as a shocking dream or nightmare . . . [and] with upsets caused by increases in internal conflict" (p. 34).

In contrast to some who argue that there is only one type of posttraumatic stress disorder, Horowitz reaffirms the appropriateness of delayed, chronic, and acute types of posttraumatic stress disorder. He also discusses differential diagnosis of organic brain syndromes, adjustment disorders, and brief reactive psychoses.

Also, in a later chapter written in collaboration with Nancy Wilner, he suggests that the diagnosis of post-traumatic stress disorder may not be as useful in some cases. He suggests the diagnosis of posttraumatic character disorders in the case of patients who were highly traumatized during adolescence or early adulthood (e.g., combat veterans and concentration camp survivors) when "identity is not completely consolidated, and the traumatic experiences of the war become incorporated into self schemata and concepts of the relationship of self to the world" (p. 49).

Thanks to the careful revisions of *Stress Response Syndromes*, this second edition will continue to be a primary reference for scholars and practitioners interested in traumatic stress.

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Psychological Aspects of Surgery, edited by Frederick G. Guggenheim. Basel, Karger, 1986, 225 pp., \$59.25.

This book reviews surgical procedures and the complex reactions they engender. The book is divided into two sections. The first discusses psychological issues common to many surgical patients, and the second deals with psychological responses to specific surgical procedures. The chapters are varied in approach and quality.

Marie Johnston reviews the literature about the ability of preoperative emotional states to predict postoperative recovery. Many of us learned from the Janis research in the 1950s that there was a U-shaped relationship between preoperative anxiety and postoperative recovery: the best recovery was found in those who expressed a middle range of anxiety preoperatively. This has come to be accepted as "the truth," despite the fact that numerous studies have failed to replicate this finding. Instead, the studies are consistent in finding that preoperative anxiety and postoperative psychological complications are linearly related, thus adding fuel to the controversy about denial's costs or benefits. Other chapters in this section review psychological interventions with surgical patients, postoperative delirium, and psychological aspects of surgery in children.

Marcia and John Goin discuss psychological effects of aesthetic facial surgery. They point out that psychiatric morbidity was higher in older studies than more recent ones and infer that changing cultural evaluation of such surgery may be responsible. They report that depression, loosely defined, troubles about 30% of patients following face-lifts. The best predictors of such postsurgical depression were characterological patterns and preoperative depressive symptoms, as opposed to factors such as satisfaction with the operative result. Although there is a high rate of such depression, it should be emphasized that there is also a substantial improvement in morale and functioning in many patients following aesthetic facial surgery.

Stanley Heller and Donald Kornfeld review psychiatric aspects of cardiac surgery. They note that even as late as 1980 there were common misperceptions among patients regarding impending cardiac surgery (e.g., one-quarter of coronary artery bypass patients thought that the heart was removed from the body during the surgery). They note that patients often displace their anxiety and irritation onto tangential issues, such as needles or troublesome roommates and, in contrast, view their surgeon as "golden hands." Despite the improvement in angina following coronary artery bypass graft, the authors note sexual avoidance, depression, and persistent failure to return to work in a substantial portion of patients.

Albert Stunkard, Gary Foster, and Richard Grossman review surgical treatment of obesity. They view such treatment as appropriate only for those with severe obesity, i.e., 100% or more above ideal body weight. Other criteria for selection of patients for surgery include a negative history of alcoholism, drug abuse, or other psychiatric problems that might compromise the patient's cooperation. Conservative treatment of such patients has been disappointing, and the common treatment—dieting—may precipitate emotional disturbance, which then blocks further dietary adherence. In contrast, gastric bypass surgery seems relatively benign for carefully selected patients. The ensuing weight loss is associated with little emotional disturbance, a profound change in eating behavior, and even a change in food preferences.

Norman Levy reviews renal transplantation in a thoughtful, clinically useful chapter that guides the psychiatrist

unfamiliar with end-stage renal disease through the various treatment options. He points out that the decision to donate a kidney can be a complex one with numerous family reverberations (e.g., the opportunity for redemption for past hurts to the family, the wish for greater intimacy with the recipient). It is thus not surprising that donors experience postoperative blues, particularly if the graft is rejected. He also points out that there is a large amount of misinterpretation regarding implications of transplant surgery, that many patients have no accurate concept of immunosuppressant medications or understanding of rejection, and that many have the fantasy that the transplantation will essentially cure the recipient entirely. The extent of this lack of knowledge is striking and reflects a mixture of inadequate provision of information and the patient's denial.

Sheri Lundberg and Frederick Guggenheim review the sequelae of limb amputation, pointing out that patients who have had traumatic amputations often present with resentment and defiance rather than the hopelessness and despair of the amputee who has lost a limb because of disease. Other chapters review the psychological effects of hysterectomy and tubal ligation and the psychiatric sequelae of surgical treatment of breast cancer. The volume concludes with a chapter on penile prostheses written by Thomas Stewart. Stewart reviews the different surgical approaches that are used for treatment of impotence, noting that psychogenic impotence is not necessarily a contraindication for such procedures.

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### **NEUROSCIENCE**

The Catecholamines in Psychiatric and Neurologic Disorders, edited by C. Raymond Lake, M.D., Ph.D., and Michael G. Ziegler, M.D. Stoneham, Mass., Butterworth, 1985, 332 pp., \$35.95.

This slim, attractively composed, but somewhat overpriced volume provides a summary of a broad range of contemporary clinical metabolic and pharmacologic research on catecholamines pertinent to selected neuromedical and psychiatric disorders. For a multiauthored (N=33) and highly specialized work, the editors have done an admirable job of maintaining fair stylistic consistency, yet there is some repetition and only limited cross-referencing between chapters. The bibliographies are generally good but are not authoritative (they are selective and contain some errors). Chapter summaries are an excellent idea but vary in style, clarity, and utility. The entire book would have been helped by an overall final summary to place minutiae into a broader theoretical and critical perspective.

The perspective is clearly Bethesda-oriented and heavily influenced by an approach to contemporary biological psychiatry in which the National Institute of Mental Health (NIMH) intramural program largely dominated the field in the United States from the late 1950s into the 1970s. Most of the contributors are or were trainees or staff investigators at NIMH and the nearby Armed Services University for the Health Sciences. Many of them have been moving out into the university-based academic community—a healthy and long-needed trend. Evidence of "Bethesdacentricity" is the domination of this volume by norepinephrine and its assay in plasma and other body fluids, in which members of the

NIMH intramural staff (including several of the authors) have made seminal technical contributions and clinical applications.

The book is most stimulating and upbeat in chapters with an adrenergic-cardiovascular orientation, including the preface and section one, Stress (pp. 1-72), plus chapters four and six in section two, Neuropsychiatric Disorders. Some chapters on other neuromedical topics are wan and unconvincing (chapters five, seven, and eight) or overloaded with details of rather parochial experience (chapters four, six, and 10). There is a tendency to lump together both sound and methodologically insecure studies and to emphasize specific data without sufficient critical analysis and integration into contemporary neuroscience and broader aspects of clinical research in psychiatry. The important methods-oriented preface is surprisingly superficial in its description and analysis of assay methods, and its content is not well integrated into subsequent chapters concerning studies using these methods. Although the level of scholarship and editing are generally good, there are occasional jarring gaffes (e.g., misspelling the names of several heroes in the field—Irwin J. Kopin [p. xvi], Arvid Carlsson [p. xvii], and Seymour S. Kety [p. 309]; describing descending prefrontal cortical catecholamine tracts that have not yet been discovered [pp. 97-98]; and calling imipramine a powerful blocker of the uptake of dopamine [p. 201]). Other nits could be picked as well, but suffice it to say that this book will be of most interest and help to research specialists rather than to general psychiatric readers.

The chapters of particular psychiatric interest in sections four (Affective Disorders) and five (Schizophrenia) are strikingly downbeat, despite more than three decades of vigorous and expensive research by talented investigators. Mercifully, much of the bad news (about negative or inconclusive research) is summarized in several good tables and a telegraphic, annotated-bibliography style. For example, the lack of a consistent, theoretically compelling, and clinically helpful pathophysiologic role for the catecholamines in major depression is emphasized in such statements as, "We continue to view the applications of all these measures as appropriate to clinical experiments and not to clinical practice. . . . Our ability to biochemically subtype the major . . . syndromes of . . . depression is rudimentary" (p. 227). "The studies cited . . . present an inconsistent and even paradoxical picture of noradrenergic function in the affective disorders" (p. 247). Similarly inconclusive or dour (p. 323) characterizations are offered with respect to clinical evidence concerning a role of norepinephrine or dopamine in schizophrenia (pp. 302-303). It is surprising to see the number of small, "preliminary," and inadequately controlled clinical studies that continue to appear in this field. One longs for more definitive critical studies involving large numbers of clinically pertinent subgroups of subjects-studies of the kind for which NIMH may still be best suited. Although the technical and basic scientific contributions of catecholamine research in neuropsychiatry have been prodigious, this book illustrates the remarkably mixed and inconclusive picture of its contributions to clinically helpful advances in the study of major idiopathic psychiatric disorders.

An important view well represented in this book is the growing realization that the pharmacocentric search for causes of idiopathic psychiatric disorders based on drug actions has been painfully simplistic and perhaps logically risky. There is an emerging tendency to view metabolic and other biologically defined features, frankly, as symptoms and not necessarily as clues to critical aspects of pathophysiol-

ogy, let alone causes, of idiopathic major psychiatric syndromes (e.g., bipolar disorder and panic-agoraphobia) and protosyndromes (e.g., major depression and schizophrenia). Credible clinical research in biological psychiatry requires more than a new assay method and samples of body fluid. Indeed, the pertinent discussion in several sections of this book of nosological and semantic problems in selecting patients who might be expected to fall into biologically coherent groups is most welcome (e.g., chapters nine and 12).

Of possible additional interest to readers of this book are a masterful review of its field by Irwin Kopin (1), one of the major generative forces in this field at NIMH, and the awesome compendium on affective disorders edited by current and past "Bethesdaniks" Robert Post and James Ballenger (2). For a more gossipy sociological view of the NIMH dynasty in contemporary neuroscience and biological psychiatry, there is a new book by Robert Kanigel (3). Overall, I give *The Catecholamines in Psychiatric and Neurologic Disorders* a 200 rating on the NIMH grant-evaluation scale and recommend it for knowledgeable and skeptical readers.

#### REFERENCES

- 1. Kopin IJ: Catecholamine metabolism: basic aspects and clinical significance. Pharmacol Rev 1985; 37:333–364
- Post RM, Ballenger JC: Neurobiology of Mood Disorders. Baltimore, Williams & Wilkins, 1984
- 3. Kanigel R: Apprentice to Genius. New York, Macmillan, 1986

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Neuropharmacology of Scrotonin, edited by A. Richard Green, M.R.C. New York, Oxford University Press, 1985, 420 pp., \$35.00.

Serotonin is one of the most important brain neurotransmitters. Such specific behaviors as mood, sleep, appetite, sexual function, pain sensitivity, circadian rhythms, temperature regulation, motor activity, and memory, which are disturbed in various psychiatric disorders, are in part dependent on serotonergic neurotransmission. Deficiencies in serotonergic neurotransmission have been linked to depression and mania especially but are also thought to be relevant to suicide, violence, Alzheimer's disease, schizophrenia, anxiety disorders, obsessive-compulsive disorder, and anorexia nervosa. These are only the most important neuropsychiatric conditions that have been related to abnormalities in serotonergic transmission; others have also been related. In addition, antidepressants, lithium, and ECT have profound and diverse effects on serotonergic neurotransmission, and there are reasons to believe that at least some of these effects are highly important to their therapeutic action. For these reasons, it behooves psychiatrists to know as much as they can about serotonin and to be in a position to follow developments in this rapidly moving field. Specifically, new laboratory procedures such as determination of platelet serotonin uptake and imipramine binding sites, which modify the serotonin uptake process, may have diagnostic utility, and new drugs to treat depression and anxiety (e.g., fluoxetine, a serotonin uptake blocker, and buspirone, a serotonin agonist) are expected to be available shortly.

Neuropharmacology of Serotonin is an excellent resource book for anyone interested in review articles covering the major basic science aspects of serotonin physiology and psychotropic drugs. Its 14 chapters are authoritative, comprehensive, clearly written, and as up-to-date as one can expect. Reviews of this depth are not available in a single source anywhere else.

The chapters of greatest interest to psychiatrists might be Briley's review of imipramine binding, Leysen's chapter on serotonin receptor binding sites, Ogren and Fuxe's chapter on the effect of antidepressant drugs on serotonin receptors, DeMontigny and Blier's discussion of the electrophysiological effects of antidepressants on serotonin neurons, Gardner's discussion of the role of serotonin in animal models of anxiety, and the editor's summary chapter on current research on serotonin and its clinical implications. Other chapters cover serotonin synthesis and metabolism, second messengers for serotonin, serotonin neuron electrophysiology, serotonin and hallucinogenic drugs, and effect of serotonin on rodent and invertebrate behaviors.

Some of the clinical implications of current serotonin research are worth noting here to help to understand the importance of this material. Multiple serotonin receptors have been identified by using classical techniques such as in vitro binding and in vivo pharmacological stimulation and antagonist studies. The full catalog of serotonin receptors is not yet known; there are still significant gaps in the pharmacologic armamentarium needed to define even the known receptors, e.g., specific antagonists for 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors. Buspirone, a novel anxiolytic whose mechanism of action was at first a mystery, was found to be an extremely potent 5-HT<sub>1A</sub> agonist. None of its other pharmacological effects appears to be related to its anxiolytic properties. Further research with this and related compounds could profoundly modify current theories of what causes anxiety and how all anxiolytic drugs act. Another important clinically significant finding is that antidepressant drug treatments and ECT produce profound changes in 5-HT<sub>2</sub> ligand binding site number—but in the opposite direction! Most studies suggest that both enhance serotonergic neurotransmission, however. What is the relationship between ligand binding studies, true receptor changes, and functional effects? Finally, in view of the evidence for the importance of other neurotransmitters such as norepinephrine, dopamine, and acetylcholine for depression, studies reported in this book that reveal reciprocal influences of these on each other are of special interest. One of the most intriguing aspects of this whole story is how a serotonin deficiency may be related to both depression and mania and why drugs that enhance serotonergic neurotransmission could have both antidepressant and antimanic effects.

In summary, this is a good starting place for serious students of serotonin research, especially the many residents, fellows, and junior faculty who should be contemplating initiating research in this important and exciting area.

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Fundamental Neuroanatomy, by Walle J.H. Nauta and Michael Feirtag. New York, W.H. Freeman and Co., 1986, 329 pp., \$39.95; \$26.95 (paper).

For the average psychiatrist the word "neuroanatomy" triggers a cascade of long-suppressed memories. We recall the smell of brains in formalin, devilishly complex diagrams, unintelligible photographs, and the fear that the examiner,

intuiting our Achilles heel, would demand a discussion of some tract or nucleus. The nature of our practice and the abundance of colleagues in neurology have allowed most of us, thinking of the brain as a black box, to survive quite well once the Board examinations are over. Such a position may soon become less tenable. Recent scientific advances have led to increasing delineation of biological substrates mediating not only the major psychiatric illnesses but much of human behavior. In the future it is likely that we will need more, not less, understanding of the brain's structure and function.

Nauta and Feirtag's book is not only a cursory survey of where neuroanatomy has been since we left medical school but a second chance to understand if not to learn the basics. The title *Fundamental Neuroanatomy* does not do the book justice because, as the authors acknowledge, the text includes elements of all the neurosciences—from physiology to embryology. It is a fundamental approach that "assumes no special knowledge on the part of the reader." The body of knowledge is virtually built from the ground up.

The authors lead with a gentle discussion of the phylogeny, anatomy, and function of the neuron and set the tone for the book as a whole. It presumes an inquisitive reader and leads him or her to develop an understanding rather than a factual catalog of the CNS. It is a story, not an encyclopedia. Current knowledge of the CNS is interwoven with the history of its discovery. Facts appear as solutions to a puzzle. Etymology is explained. The text moves languidly at times but is eminently readable. The neurons join in connecting nets, and we are gently introduced to neural pathways that gradually increase in complexity. Connections of systems like the limbic or sympathetic are related to function. The schematic diagram of the CNS that appears repeatedly with different pathways highlighted is initially intimidating, and one might have wished that the various connections appeared as they were introduced, but it does in the end convey a sense of the CNS as a whole.

It is not until almost halfway through the book that neuroanatomy as we knew it—represented by schematic cross sections, black and white photographs, and eponymic cell groups—appears. We move along the spinal cord, through the brainstem, and upward. Although the photographs and diagrams lighten the task, the reader must adopt a slow pace and then retrace his or her steps several times. The organization of the brainstem is complicated, but effort expended to understand it is gradually rewarded.

The authors cleverly introduce the cerebral hemispheres by building them up schematically from the inside out in five steps. The maneuver is a welcome one because, as is usual in this book, the basic structure becomes easy to understand as well as remember, and it provides a reference point for further discussion. The atlas of cross sections of the forebrain contains clear color photographs and corresponding schematic diagrams that are as good as can be wished for. It is a pleasure to move with facility from the schematic to the photograph and not have to wonder whether the thalamus is indeed where the diagram shows it to be. Although the accompanying narrative demands careful reading, the pace is lightened by a sprinkling of clinical correlates and historical anecdotes, such as the one about how the substantia innominata got its name.

The cerebellar cortex and neocortex, respectively, are presented near the end. Recent discoveries such as the columnar organization of the visual cortex and its functional implications are noted. In the final chapter the authors raise questions for the future that range from the clinical to the metapsychological. They also reinforce a familiar theme—

that the basic wiring of the CNS, which appears so elegantly straightforward in their diagrams, belies a complexity that taxes the imagination. It reminds us that we are but in the infancy of neuroscience. The unspoken warning is against excessive and premature reliance on simple models of brain function.

The authors have tackled a difficult area and made it accessible while conveying an appreciation of its complexity. Using narrative, they provoke as well as anticipate questions, weaving tales of discovery into the fabric of facts. By engaging our curiosity and sense of wonder they dissipate much of the expected tedium. The discussions of functional subunits, such as cranial nuclei and cortical areas, have a clinical bent but a gentle one. The book does not pretend to supply the clinical or scientific detail in neuroanatomy that the specialist will need. However, the medical student, the psychiatric resident, and any of us who feel the need to brush up and catch up will find it not only invaluable but surprisingly readable.

Nauta and Feirtag set out to provide the reader with a basic understanding of CNS structure. Their vehicle is a well-written book that engages as it instructs. It will be a most welcome aid to anyone needing a neuroscientific introduction to human neuroanatomy.

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Neurotransmitter Receptor Binding, 2nd ed., edited by Henry I. Yamamura, S.J. Enna, and Michael J. Kuhar. New York, Raven Press, 1985, 256 pp., \$54.00.

This text is becoming a classic in the field of neurotransmitter receptor binding. It is written as a guide to laboratory analysis rather than as a treatise on theories of neurotransmitter receptors. As such it is practical, readable, and straightforward, combining concise discussions of theory with precise instructions on the performance of assays. Even more important are the sections on data analysis, which clearly explain the rationale behind the equations used to analyze results of the assays.

The editors have organized the book so that various chapters may be read independently, depending on interest. The first three chapters provide background on issues involved in studying receptors and should be read by everyone reading the book. The chapters that follow are filled with specifics of analysis, applicable to those with interests in the various techniques. New to this edition are chapters on peptide receptor binding and ion channel binding as well as illustrations on the use of DNA technology in studying receptors.

This book will continue to be of great use to investigators involved in receptor binding work. For those who have read the first edition, the book has been updated with the latest in technology and thought. For the reader with little background in receptor binding, the book is a perfect introduction, with enough theory to facilitate understanding and specific instructions on how to perform and interpret various assays. Receptor binding studies are being applied to psychiatric research more frequently and this book will help us all to understand the strengths and pitfalls of this exciting neuroscience technique.

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### **ALCOHOLISM**

Recent Developments in Alcoholism, vol. 4, edited by Marc Galanter. New York, Plenum, 1986, 453 pp., \$59.50.

Each volume in this series is structured in the same manner and covers four topics related to alcoholism. Each topic is introduced by a section editor, followed by four or five chapters by different authors. This structure is logical and frequently is sufficient to give comprehensive coverage to a topic without being repetitive if the section editor gives the authors adequate direction. In this volume, the editors have been reasonably diligent.

The first section is concerned with combined alcohol and drug abuse problems. An excellent opening chapter reviews the difficulties in measuring the presence, correlates, and consequences of multiple drug abuse. The important point is made that multiple drug abuse is widespread but underrecognized and that the current concentration on single abuse models does not accurately reflect clinical realities. Another chapter in the section argues that all abusers, after detoxification, should be treated by the same methods and personnel. Although logical reasons are given for this view, no data are presented to support it. The other two chapters in this section concern the pharmacological and clinical effects of combining sedative-hypnotics (including alcohol). These chapters clearly present what is known about these interactions while lucidly discussing the difficulties in researching the effects of such drug-drug interactions given the large number of possible combinations and variables. A weakness of this section is that it has only a cursory discussion of alcohol in combination with stimulants, marijuana, hallucinogens, opiates, or tobacco.

The second section contains four chapters on typologies of alcoholics. This is an increasingly important area of alcoholism research and is concerned with methods of classifying alcoholism into various subtypes. The hope of this research is that specific subtypes will be related to specific etiologies, prognoses, and/or responses to treatments. Each subtype could then be treated with a specific therapy, in contrast to the current practice of every patient receiving essentially the same treatment, which is of limited effectiveness. The opening chapter is an interesting review of English, German, French, and American typologies of alcoholism used in the nineteenth and twentieth centuries. This chapter highlights the fact that many of the problems currently facing typological systems were recognized in the past. Three chapters discuss various issues in current alcoholism classification research. One of the issues is whether categorical (each subtype is distinct and discrete) or dimensional (each subtype is on a continuum with other subtypes) models are more appropriate. Another is whether empirical (dividing types by the results of some measure such as the MMPI, for example) or theoretical (dividing types into categories presumed a priori to differentiate between alcoholics, such as sex and family history) approaches are more fruitful. Still another is whether cluster or factor-analytic statistical methods are better at dividing alcoholics in a clinically relevant manner. There is also a chapter discussing the subtyping of alcoholism by the co-occurrence of hyperactivity, antisocial personality, and a family history of alcoholism. This chapter concludes that subtyping by the last two factors may distinguish alcoholics in terms of severity and course of alcoholism, response to treatment, and age at onset of problem drinking. This section gives the sense of much ferment and activity and increasing attention being given to clarifying

research questions, problems, and methods. Whether such typologies lead to clinically relevant results, such as differential treatment, remains to be seen.

The third section reviews aspects of the alcohol withdrawal syndrome. The first two chapters discuss the effects of alcohol intoxication, tolerance, and withdrawal on cellular membranes, neuroendocrine systems, and neurotransmitter levels. These chapters are succinct, current, and well referenced. The final two chapters of this section review clinical aspects of alcohol withdrawal, including symptoms, assessment methods, pharmacological and nonpharmacological treatment, and management of special problems such as withdrawal occurring with medical, psychiatric, and/or other substance abuse problems. Both chapters are scholarly, cogent, and practical.

The final section concerns renal and electrolyte consequences of alcohol abuse, a topic usually given only cursory attention in most discussions of alcoholism. The section's four chapters were written by the same two authors, which gives them a coherence that is of value in this somewhat technical area. Much of the section is devoted to renal and electrolyte problems seen in the cirrhotic patient with ascites, although problems encountered in the acute and chronic noncirrhotic alcoholic are also covered. These chapters are very well referenced, thorough, and lucidly written and will serve well as the standard review of this topic.

In summary, although not every section of this book is of interest to every potential reader, each topic is covered in sufficient depth, currency, and clarity to be of value to the neophyte and the seasoned researcher/clinician. This volume, in conjunction with the others in the series, continues to live up to the intent of the series "to span the breadth of research from epidemiological and preclinical issues to ones of clinical management."

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Research Advances in Alcohol and Drug Problems, vol. 8, edited by Reginald G. Smart, Howard D. Cappell, Frederick B. Glaser, Yedy Israel, Harold Kalant, Robert E. Popham, Wolfgang Schmidt, and Edward M. Sellers. New York, Plenum, 1984, 333 pp., \$49.50.

This volume is the eighth in the Research Advances series edited by a distinguished group of investigators from the Addiction Research Foundation of Ontario. This volume is described as an omnibus rather than a theme volume and includes research on alcohol, opiates, and tobacco. There is no connecting bridge between the chapters, and each chapter really stands alone. Taken as a whole, the volume will be of limited interest to practicing psychiatrists, even those with a substantial interest in clinical aspects of the substance abuse

The opening chapter by Prof. Lars Terenius on opiate tolerance and dependence includes an excellent review of the past decade of research on opiate receptors and the homeostatic regulation of endorphin systems. Among other major points, Terenius indicates that despite more than a decade of research, there are no available experimental data suggesting changes in the gross number of receptors or overall peptide levels as a consequence of chronic opioid treatment. This may be because "both receptors and peptides may occur in such surplus that changes become unobservable." Terenius urges studies of regional brain differences in peptides and

receptor function in response to chronic opioid administration to attempt to relate tolerance and physical dependence

to changes in neurochemistry.

The chapter by Deitrich and Spuhler provides an excellent review of the genetics of alcoholism and alcohol's actions in human populations and animal models. Deitrich is a pharmacogeneticist, and his review of both human and animal studies represents a scholarly state-of-the-art analysis of a very complex area of active investigation. Skinner's paper on assessing alcohol use by patients in treatment is a very useful primer that should be required reading in alcohol treatment programs and general medical settings. He clearly differentiates between assessment of alcohol consumption, alcohol dependence, and alcohol-related disabilities in a way that is seldom applied adequately in treatment settings. Skinner reviews the data on a variety of research instruments and various biochemical markers that have been used to assess alcohol consumption.

Finally, Vaillant offers another of his well-written statements that emphasize psychopathology as a consequence of alcohol addiction. He cites data from a variety of longitudinal studies that minimize the importance of psychopathology as a risk factor for the development of alcoholism. It is somewhat paradoxical that Vaillant, again in this chapter, emphasizes genetic etiology and minimizes any risk associated with antisocial personality disorder or other personality abnormalities, while Cloninger (who has worked in the area of population genetics) has recently emphasized the importance of certain personality variables as risk factors for the development of alcoholism. The relationship between alcoholism and psychopathology is obviously complex.

Other chapters in the book will not be as interesting to psychiatrists. There are chapters on less hazardous tobacco use as a treatment for health-related problems associated with smoking, epidemiological and other studies of driver impairment and alcohol-related collisions, alcohol consumption and ischemic heart disease, epidemiological evidence on the effects of heavy alcohol consumption on physical health, and alcohol self-administration by experimental animals. The advantages of this book, as part of this larger series, is that the authors have the opportunity to speculate more freely than they might in peer-reviewed journal articles. Although there are pros and cons to this, the distinction of the authors assures a quality product in each chapter. Unfortunately, the heterogeneity of subjects in this particular volume probably limits its overall usefulness to our specialty.

> ROGER E. MEYER, M.D. Farmington, Conn.

### CHILD PSYCHIATRY

The Clinical Guide to Child Psychiatry, edited by David Shaffer, Anke A. Ehrhardt, and Laurence L. Greenhill. New York, Free Press, 1985, 604 pp., \$45.00.

This excellent book addresses a variety of needs within child psychiatry. In size it occupies a middle ground between comprehensive textbooks such as Child and Adolescent Psychiatry (1) and the Basic Handbook of Child Psychiatry (2) and the various brief, usually paperbound, synopses. It successfully attempts to provide a comprehensive update from a unique perspective: it not only catalogs the scientific

advances of the last 15 years but also demonstrates how they inform modern clinical practice. It is perhaps closest in mission to the child psychiatry units of the third and fourth editions of the Comprehensive Textbook of Psychiatry (3, 4); however, these units must necessarily cover a wide breadth of topics. The Clinical Guide to Child Psychiatry takes a new tack. In the first of its three units, the editors have selected as chapter topics a broad, although not encyclopedic, list of clinical disorders that form the bulk of contemporary child psychiatric practice. They have then assembled a group of distinguished authorities to address these topics in detail. Among these are included Michael Rutter, whose chapter on autism deserves special commendation; Donald Cohen, James Leckman, and Bennett Shaywitz on Tourette's disorder and tics; Paul Ambrosini and Joaquim Puig-Antich on depression; Judith Rapoport; Katherine Halmi; Dorothy Otnow Lewis; and many others.

Whether by intent or coincidence, the editors have repeatedly identified areas in which practitioners frequently feel a need for an update and reorientation. All of the chapters maintain a strong clinical orientation; the scientific material that is presented, although usually quite comprehensive, is always addressed from a perspective of clinical utility. I was regularly struck by the way each chapter naturally lends itself to an understanding of the comprehensive diagnosis and management of the disorder addressed.

The first unit alone would make this a valuable book. However, the editors have produced two more units of comparable worth. Part two, Evaluating Problems-The Diagnostic Approach, is a masterful summary, in a little over 100 pages, of a comprehensive and modern approach to the diagnostic assessment of all children. Part three, General Notes on Treatment Approaches, addresses the current state of the art of pharmacotherapy and several psychotherapies of children. It does not presume to be a comprehensive treatment of these subjects but succinctly identifies current trends and controversies of interest to practitioners.

This is a superb book, made up of contributions from knowledgeable and articulate authors. Its topics have been selected thoughtfully to address the needs of clinicians in general rather than the special interests of particular scholars. The editors and contributors are to be commended for a remarkable consistency of good writing, characterized by both authority and clarity. The typeface, subheadings, and physical layout of this book also make it eminently readable.

The Clinical Guide to Child Psychiatry will be useful to many readers. In general, it presupposes some basic knowledge of children's development and behavior; readers who are very inexperienced in this area may wish to begin with one of the synopses or perhaps the child psychiatry unit in the fourth edition of the Comprehensive Textbook (4). Both pediatricians and nonmedical mental health professionals will find this book a good orientation to contemporary child psychiatry, and child Fellows will value it as they begin their work with children. Professors and training directors will find it a useful syllabus and teaching guide, and I suspect it would be an excellent text for Board examination review. But it may be welcomed most of all by those of us already in clinical practice, whose training reflected the more traditional strengths of our discipline. We will use this book to augment our experience with an accessible introduction, actually more than an introduction, to much that has come forth in recent years for the benefit of our patients. The bookshelf containing this text alongside Rutter and Hersov (1) for scientific detail and the Basic Handbook (2) for traditional wisdom will be well endowed.

### REFERENCES

- 1. Rutter M, Hersov L (eds): Child and Adolescent Psychiatry, 2nd ed. Oxford, Blackwell Scientific Publications, 1985
- Noshpitz JD (ed): Basic Handbook of Child Psychiatry, vols 1–4. New York, Basic Books, 1979
- Kaplan HI, Freedman AM, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 3rd ed, vols 1–3. Baltimore, Williams & Wilkins, 1980
- Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vols 1, 2. Baltimore, Williams & Wilkins, 1985

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Psychopathology of Childhood: A Clinical-Experimental Approach, 2nd ed., by Steven Schwartz and James H. Johnson. New York, Pergamon Press, 1985, 456 pp., \$24.50.

This text has been written to provide readers with current knowledge about child psychopathology. The book has 11 chapters, beginning with an introductory chapter on the historical, theoretical, and methodological issues in children's psychopathology. This is followed by chapters that discuss assessment, common developmental problems, schizophrenia, brain pathology, "neurotic" disorders, psychological factors and physical disorders, cognitive disorders, juvenile delinquency, psychological approaches to child treatment, and a final chapter on the prevention of child psychopathology. Clearly, the authors have conscientiously covered all the major areas in child psychopathology. Although such comprehensiveness is commendable, it might also be a weakness in that no one topic is covered in substantial depth.

The authors stress that they want to provide students with a greater appreciation of the importance of developmental variables in child psychopathology. In this effort they have been successful. The major theories and principles of child development are discussed in chapter one, and the developmental implications for each area of children's psychopathology are presented throughout the text. The authors also state in the preface that it is their intention to stress research rather than to present clinical material. Here, too, they are true to their goal. They discuss the major theories and research associated with each area of psychopathology and evaluate the current state of the research that is now being done, although this is weighted more toward psychology than psychiatry; they also make concrete suggestions for improving future research studies. In this regard, their chapter on intellectual and cognitive disorders is exemplary. They have written a particularly provocative account of the issues and problems associated with investigating children's cognitive development. This chapter is a must for anyone interested in doing research in children's typical and atypical cognitive development.

It is difficult to decide what type of reader would most benefit from this text. The authors recommend that the reader have some working knowledge of psychology, and we would further suggest that readers have some knowledge of research methodology to be able to keep pace with rapid-fire presentation of facts and to understand the subtleties of the authors' research analyses. This text has really been written by psychologists for advanced psychology students and for professionals with some psychology background. For clinical

child psychiatrists or other psychiatrists interested in child psychopathology, the depth is similar to that found in the child psychiatry sections of the major adult psychiatry texts, although the research issues are better articulated here.

In summary, since the book does not cover the topics involved in child psychopathology in sufficient depth, it is probably not an appropriate choice for a classroom text-book. However, for individuals with some psychology and research methods background, it is an excellent resource and reference book that provides a comprehensive overview of the current developments and research issues in the major areas of children's psychopathology. The text contains excellent summary references for readers who want to pursue a topic in greater detail.

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Low Achieving Children: The First Seven Years, edited by Sarah H. Broman, Ellen Bien, and Peter Shaughnessy. Hillsdale, N.J., Lawrence Erlbaum Associates, 1985, 170 pp., \$19.95.

Learning disabilities have been difficult to define and treat, yet several strongly held theories for their genesis have been promulgated. Meager facts are a fertile bed for intense advocacy concerning causes and outcomes. It has become commonplace to encounter descriptions of specific causes of learning disabilities and to find all manner of behavioral, emotional, cognitive, social, and vocational problems ascribed to the presence of learning disabilities. This occurs with an aura of finality, dismissal of further responsibility for evaluation, relief that other complex factors do not contribute, and the sense that a highly specific phenomenon has been identified that determines a correspondingly specific treatment. Unfortunately, learning disabilities typically come packaged in a great deal of ambiguity and in the company of multiple influences that could lead to similar outcomes. The myths generated by the tendency to oversimplify can interfere with the willingness for diligent work required to establish the facts. This excellent book uncovers myths as it reports on learning disabilities as an outcome in a wellconceived, meticulous, prospective study. This accomplishment is not the final perspective on this problem, however, because the research design suffers from limitations that were unavoidable at the time it was initiated. New research is underway that should help alleviate the fear that new myths will arise in place of the old.

Estimates of the prevalence of learning disabilities among school-age children vary from 2% to 20%, clearly a very large number of children. This broad range reflects difficulties defining the problem. Most clinicians agree that a specific learning disability is present when a youngster shows a marked discrepancy between his or her achievement level and age and intellectual ability (when the child has had access to an appropriate learning environment and there is no obvious cause for his or her poor performance). Rendering this into a more specific operational definition has been difficult. To make matters worse, related concepts and disorders, such as dyslexia, minimal brain dysfunction, hyperactivity, attentional dysfunction, and conduct disorders, overlap the construct of learning disabilities and resist easy definitional separation. These ambiguities are paralleled by the presence of multiple etiological theories, including genetic influences, perinatal complications, psychological factors, family characteristics, language impairments, and the ill-defined "maturational lag." In this context of confusion a substantial group of clinicians and investigators came to view complications in pregnancy and the perinatal period as determinants of an underlying brain damage that caused later learning disabilities. This reflected the sensible theory of a continuum of reproductive casualty: abnormal intellectual, language, and behavioral sequelae of increasing severity that correspond to a comparable gradation of brain damage.

The Collaborative Perinatal Project, begun in 1959, provided an opportunity to examine the consequences of complications during pregnancy and the perinatal period. Research teams in 12 medical centers followed 34,875 children from 53,043 pregnancies through 1974, from their mothers' pregnancy through 7 years of age. Abnormal outcomes of central interest were cerebral palsy, mental retardation, congenital malformations, and learning disorders. This book reports on the antecedents and symptoms of children with learning disorders. "Low achievers" were defined by IQ scores of 90 or above at age 7 and achievement levels more than 1 year below grade placement in reading or spelling. This generated a sample of 994 low-achieving children (about 3% of the children in the population sample) to which control groups six times as large were matched for age and IQ scores. Subgroups were formed by sex, race, extent of academic impairment (indicating a lower-achieving subgroup), cognitive level (low-, middle-, and high-IQ subgroups), reading skills (the poorest readers), and behavior (the hyperactive children). Comparisons between control and subject groups then were carried out in the domains of prenatal and perinatal characteristics, neurological signs, verbal and perceptual-motor abilities, family characteristics, and other possible etiological factors or correlates.

Expectations of the project planners concerning the outcome of this mammoth enterprise are clear. As Dr. Arnold Sameroff indicates in his fine introduction to the monograph, of the 169 variables examined, 161 described the medical and developmental characteristics of the mother and child. Although only eight variables pertained to family characteristics, it is fortunate that the protocol planners had the prescience to include them. The outcome of the research supports results emerging from other groups of children studied: low academic achievement is related to "lower socioeconomic status, less maternal education, higher birth order, and larger family size." In further agreement with earlier research, most of the children with learning disabilities were boys, and an association between poor academic performance and behavioral problems was observed. Among the lower-achieving subgroup, behavior problems were more

prevalent among whites and physical problems (a hearing deficit in 1% and suspicious neurological findings) more common among blacks. When the lower-achieving subgroup was examined separately, gestational and perinatal complications played a role, particularly among girls. For the larger group, however, the authors make the clear statement that "although biological factors were identified as antecedents and correlates of low achievement, they were diffuse and relatively weak as discriminators."

This is a spare book, given neither to literary ornamentation nor to a broad theoretical discussion of the study's outcome. This reflects the conservative title of the book, which avoids the term "learning disabilities," and is as it should be in a report of the Collaborative Perinatal Project, which is such a significant contribution to our understanding of developmental pathology. There will always be discussions of how it could have been done better, regardless of realistic limitations at the time of its initiation. The terse style-short chapters focused on findings for specific subgroups and related topics, tables crammed with facts, a brief review of each table—creates a book difficult to read coverto-cover without losing one's way occasionally. Yet it constructs a record that will be examined frequently by anyone interested in vulnerable children, learning disabilities, and development in early childhood.

The overall outcome may have surprised the planners of this important research project. The molding influence of the environment is again affirmed, and it is obvious that medical concerns about morbidity among vulnerable children merge into the socioeconomic concerns of our communities. Yet we must be cautious to avoid further entrapment by bias. More sophisticated technology now makes it possible to select better differentiated subgroups of infants, especially through new imaging methods. Associations among gestational and perinatal events and later intellectual and behavioral outcomes in the larger group of vulnerable children were likely to be washed out; on the other hand, better selected subgroups (e.g., those with hemorrhage defined by ultrasonography) have a higher probability of demonstrating these associations. A sensible model reflecting our current knowledge would describe the effects of brain damage and environmental influences in early childhood as additive and interactive. There are no simple formulas for the fluid development of the first years of life. Knowing this, physicians face formidable challenges for the children in their offices, just as we all do for the children in our neighborhoods.

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Reprints of Book Forum reviews are not available.

### Letters to the Editor

### Treatment of an Anorexia Nervosa Patient With Fluoxetine

SIR: Patients with chronic anorexia nervosa and bulimia often present difficult clinical management problems. In addition to being biologically predisposed to depression, after years of self-induced vomiting, laxative abuse, and self-starvation with eccentric dietary predilections they may be metabolically and/or neurochemically compromised. The treatment of these patients with antidepressant medications has been well documented (1). Each new antidepressant investigated has held out hope for greater efficacy. Unfortunately, two have recently been withdrawn from the market because of serious side effects (2, and unpublished manuscript by R.G. Horn et al., "Treatment of Bulimia With Bupropion," 1987). The following case history illustrates the sequential treatment of one patient with multiple conventional and "novel" antidepressants and an eventual positive response to fluoxetine.

Ms. A, a 42-year-old single white woman, presented a lifelong history of eating problems. Her compulsive overeating began at age 14. She had an episode of anorexia at age 15 and then became obese by age 17. Multiple hospitalizations for bulimia and anorexia nervosa followed during a subsequent 25-year history of unsuccessful treatment that included trials of lithium carbonate, imipramine, doxepin, amitriptyline, amoxapine, trazodone, phenelzine, tranylcypromine, and thioridazine. Ms. A could not tolerate the side effects of the monoamine oxidase inhibitors (MAOIs), and she was not helped by the tricyclic antidepressants. She was prescribed nomifensine, to which she had both an antidepressant and an antibulimic response. Unfortunately, she developed a persistent fever, which remitted when the drug was discontinued. In a double-blind study, while she was at a normal weight, she was prescribed bupropion, to which she responded very favorably. After 3 weeks of treatment, however, she suffered a grand mal seizure, possibly by activating an old, silent parietal lobe infarction caused by trauma 16 years previously. Despite her desire to continue on the medication because she had the first total relief of her symptoms in 28 years, it was decided that, even with phenytoin, a rechallenge with bupropion could not be justified.

Ms. A, at this point 15% underweight, was started on fluoxetine in a humanitarian protocol, and the dose was increased over a 2-week period to 80 mg/day without major adverse effects. Within 3 weeks she was free of her bulimic symptoms, her mood had markedly improved, and she had gained 6 lb. without dietary prescription and without psychotherapeutic intervention. Her food preferences broadened considerably during this time.

This case indicates the need for multiple trials of medication before achieving a successful therapeutic outcome in patients chronically afflicted with eating disorders. It also emphasizes the relative safety of fluoxetine. This patient was intolerant of the side effects of MAOIs, was not helped by tricyclic medication, developed a drug fever with nomifensine, and had a seizure with bupropion. Fortunately, she responded to fluoxetine; she was still doing well after 12 months of treatment.

#### REFERENCES

- Herzog DB: Antidepressant use in eating disorders. Psychosomatics (Suppl) 1986; 27:17–23
- Nassr DG: Successful treatment of bulimia with nomifensine. Am J Psychiatry 1986; 143:373–374

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### Relief of Obsessive-Compulsive Symptoms by LSD and Psilocin

SIR: An unusual case of a patient with both obsessive-compulsive disorder and multiple substance abuse provides strongly suggestive support for a role of the serotonin system in obsessive-compulsive disorder.

Adam, a 17-year-old white high school senior, had severe obsessive-compulsive disorder that had begun at age 8. Since age 13, his mind had been so preoccupied by obsessive thoughts that he was unable to do any task spontaneously. All acts had to be done in a certain way and a certain number of times. He showered by lathering the soap 22 times. He was unable to walk down a corridor unless he tapped the correct amount of times on the wall and could not complete any school assignments because written alphabet letters had to end "in a certain way going up." He was acutely aware of the irrationality of these thoughts and rituals.

Since the age of 14, Adam had extensively abused drugs; he had observed three different kinds of effects on his obsessive-compulsive disorder symptoms from these substances: specific selective improvement, nonspecific improvement, and specific worsening. LSD (which he had used more than 100 times) made his obsessive thoughts slightly worse for an hour, followed by total remission for 4–5 hours. "Mushroom" (psilocin) and mescaline, which he had used about 20 times each, also made the thoughts totally disappear.

Cocaine (used more than 100 times) and amphetamine (used about 15 times) worsened the thoughts, so that he would spend hours touching the walls 22 times.

In contrast to these selective changes, cannabis, phencyclidine, barbiturates, methaqualone, morphine, codeine, and alcohol did not change the frequency or the intensity of the obsessive thoughts but just "made everything easier to bear."

The psychedelic drugs LSD, psilocin, and mescaline act on the serotonergic system, both pre- and postsynaptically, at several sites within the brain (1). Morphine, codeine, and, possibly, phencyclidine affect opiate receptors, and their effects are not thought to be primarily related to monoamine systems (2). Amphetamine and cocaine, which worsened the patient's thoughts, both release and block the uptake of catecholamines, resulting in a general stimulation of the CNS (2). Cannabis's mechanism of action is not known, but it does not act directly on monoamines (2). Barbiturates and alcohol, which are CNS depressants, affect both excitatory and inhibitory synaptic transmission, with complex CNS effects not tied directly to monoaminergic systems (2).

The reports of this patient, who had no knowledge of biochemistry, are of great interest, as they are consistent with a serotonin hypothesis of obsessive-compulsive disorder. In addition to the well-documented efficacy of clomipramine in obsessive-compulsive disorder, augmentation of clomipramine by L-tryptophan and lithium has been reported (3). Furthermore, response to clomipramine has been correlated with higher pretreatment platelet serotonin concentration (4).

#### REFERENCES

- 1. White F: Comparative effects of LSD and lisuride: clues to specific hallucinogenic drug actions. Pharmacol Biochem Behav 1986; 24:365-379
- 2. Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1985
- 3. Rasmussen SA: Lithium and tryptophan augmentation in clomipramine-resistant obsessive-compulsive disorder. Am J Psychiatry 1984; 141:1283-1285
- 4. Flament M, Rapoport J: Biochemical changes during clomipramine treatment of childhood obsessive compulsive disorder. Arch Gen Psychiatry (in press)

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### Treatment of Premature Ejaculation With Lorazepam

SIR: I should like to report the case of a patient who was recently referred to me with a complaint of premature ejaculation.

Mr. A, a 71-year-old widower, reported a lifelong history of ejaculating shortly after intromission (usually within 30 seconds). This had only become a concern when the patient began dating after his wife's death. He reported coital activity at least once weekly, seldom with the same partner. Conjoint behavioral treatment of his complaint was unacceptable because Mr. A did not have a steady sexual partner and he was unwilling to involve one of his casual acquaintances in therapy. I was aware of previous reports of ejaculatory impairment (1) and orgasmic delay (2) associated with benzodiazepine therapy. Therefore, I recommended a trial of 0.5 mg of lorazepam approximately 30 minutes before sexual activity. On the next visit, the patient reported that this dose of lorazepam delayed ejaculation until approximately 90 seconds after intromission; consequently, he had decided on his own to increase his dose to 1 mg. At this dose, he was able to delay ejaculation approximately 4-5 minutes without a detectable change in libido or erectile turgidity. When Mr. A reluctantly agreed to try not taking lorazepam, he reported the return of premature ejaculation. Readministration of 1

mg of lorazepam before coital activities restored his ejaculatory control.

I am unaware of a possible mechanism by which lorazepam might delay ejaculation, and this is the only patient for whom I have used lorazepam as a treatment for premature ejaculation. It is noteworthy that there have also been case reports of the use of both thioridazine (3) and monoamine oxidase inhibitors (4) to treat premature ejaculation. In view of the prevalence of premature ejaculation (5), controlled studies of the pharmacological treatment of this syndrome appear warranted.

#### REFERENCES

- 1. Hughes JM: Failure to ejaculate with chlordiazepoxide. Am J Psychiatry 1964; 121:610-611
- 2. Riley AJ, Riley EJ: The effect of single dose diazepam on female sexual response induced by masturbation. Sexual and Marital Therapy 1986; 1:49-53
- 3. Mellegren A: Treatment of ejaculation praecox with thioridazine. Psychother Psychosom 1967; 15:454-460
- Simpson GM, Blair JH, Amuso D: Effect of anti-depressants on
- genito-urinary function. Dis Nerv Syst 1965; 26:787-789
  5. Segraves RT, Schoenberg HW: Diagnosis and treatment of erectile problems: current status, in Diagnosis and Treatment of Erectile Disturbances. Edited by Segraves RT, Schoenberg HW. New York, Plenum, 1985

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### Identical Twins' Nonidentical Responses to Lithium

SIR: A number of studies have shown that response to lithium has genetic determinants (1-3). In a review of the literature, I could find only one report on the treatment of twins with bipolar illness. I report here the treatment of identical twins with identical human lymphocyte antigens (HLA), each of whom responded differently to lithium when treated for acute mania.

Twin A was a 19-year-old woman of Irish descent who first became depressed in October. Though the depression lingered, she was not hospitalized until May, when she became manic 1 week after beginning treatment with imipramine.

She responded to lithium and chlordiazepoxide and was discharged after 1 week on a regimen of lithium, 900 mg/ day. She was readmitted 2 weeks later, again manic after not complying with the treatment regimen. She was stabilized on lithium and thioridazine and did not develop side effects. She was discharged after 2 weeks, taking lithium, 900 mg/day (0.8 meq/liter); this was discontinued after 4 weeks. She has been asymptomatic for 3 years.

Twin B became depressed for the first time a year after Twin A had initially become depressed. She was hospitalized in December with a major depression. Treatment with nortriptyline, 75 mg/day, was initiated, and she improved, but deterioration took place after discharge, and tranyleypromine, 30 mg/day, was added to the nortriptyline. Compliance eventually ceased, and she became suicidal and was admitted again in March.

Within 10 days she had become manic, while taking the combination of nortriptyline, 75 mg/day, and tranylcypromine, 30 mg/day. Over the next 2 months she suffered from a severe relapsing mania despite continuous treatment with lithium; haloperidol, thioridazine, chlordiaze-poxide, and tryptophan were used at various times. She experienced dystonias, ataxia, akathisia, and parkinsonian symptoms during this period of time. Stability was finally achieved with a combination of lithium, carbamazepine, and molindone, but she relapsed when the carbamazepine was discontinued. Carbamazepine therapy was reinstituted, she was stabilized, and then she was discharged on a regimen of lithium, 1200 mg/day (0.93 meq/liter); carbamazepine, 800 mg/day (9.6 µg/ml); molindone, 45 mg/day; and diphenhydramine hydrochloride, 100 mg h.s. Over the next 3 months, all medications except lithium were discontinued. Lithium was discontinued 6 months after discharge, and she has remained symptom free.

Although no birth data were available, these women were raised as identical twins. HLA typing revealed both to be positive for HLA A<sub>1</sub>, A<sub>2</sub>, B44, B39, and CW5. They were negative for all other HLA antigens.

Twin B had a more serious course of illness than twin A, but the relative lack of effect of lithium in twin B is striking. The literature (1–4) would lead one to expect a similar response to lithium treatment in identical twins.

Mendlewicz (5) postulated that drug response is determined by an interaction of genetic and environmental factors. Age and medications used were environmental factors that may have contributed to the differences in lithium response in these two patients, but this remains unclear.

#### REFERENCES

- Mendlewicz J, Fieve RR, Stallone F: Relationship between the effectiveness of lithium therapy and family history. Am J Psychiatry 1973; 130:1011-1013
- Prien RF, Caffey EM, Klett CJ: Factors associated with treatment success in lithium carbonate prophylaxis. Arch Gen Psychiatry 1974; 31:190–192
- Taylor MA, Abrams R: Acute mania: clinical and genetic study of responders and nonresponders to treatments. Arch Gen Psychiatry 1975; 32:863–865
- Aden GC: Lithium carbonate versus ECT in the treatment of the manic state of identical twins with bipolar affective disease. Dis Nerv Syst 1976; 37:393–397
- Mendlewicz J: Perspectives and practical applications of psychopharmacogenetics. Prog Neuropsychopharmacol 1979; 3:155-163

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### Haloperidol as an Alternative to Lithium in Pregnant Women

SIR: Lithium is contraindicated for pregnant women because of its suspected cardiovascular teratogenic potency (1). Lithium treatment is also associated with complications during delivery, such as lithium poisoning of both the child and the mother (1). Mania and rapidly cycling bipolar disorder can be treated with haloperidol (2, 3). It has been reported that in low doses, haloperidol is not teratogenic in animals or humans (4). Also, during pregnancy and delivery, use of haloperidol seems less likely to be associated with complications than use of lithium (1, 5).

Ms. A, a 35-year-old childless married woman, presented a history of recurrent manic illness without depres-

sive periods and with a good response to lithium. Because she wished to become pregnant, she stopped the lithium and was treated instead with a low dose of haloperidol (1 mg t.i.d.). She developed no side effects, and after 6 months of haloperidol treatment in which she had no relapse, she became pregnant. A healthy girl, weighing 8 lb., was spontaneously born at term; her Apgar score was 8/10. Except for some bleeding by the mother in the postdelivery period, there were no complications. The patient's mood was normal.

This experience, as well as indications in the literature, supports the use of a low dose of haloperidol in unipolar mania (2) and in rapidly cycling bipolar disorder (3) as an alternative to lithium prophylaxis in pregnant women.

#### REFERENCES

- Källén B, Tandberg A: Lithium and pregnancy: a cohort study on manic-depressive women. Acta Psychiatr Scand 1983; 68: 134–139
- Taylor M, Abrams R: Manic states: a genetic study of early and late onset affective disorders. Arch Gen Psychiatry 1973; 28: 656-658
- 3. Lowe MR: Treatment of rapid cycling affective illness (letter). Br J Psychiatry 1985; 146:558
- van Waes A, van de Velde E: Safety evaluation of haloperidol in the treatment of hyperemesis gravidarum. J Clin Pharmacol 1969; 9:224-227
- von Beck L: Haloperidol zur Geburtserleichterung. Klinische Erfahrungen bei 1250 Geburten. Geburtshilfe Frauenheilkd 1962; 12:1519–1525

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### Pindolol and Propranolol in Neuroleptic-Induced Akathisia

Sir: β-Adrenergic blocking medications have recently been investigated as treatments for neuroleptic-induced akathisia. Lipinski et al. (1) and Adler et al. (2) have shown that propranolol (30–80 mg/day) safely and effectively treats neuroleptic-induced akathisia. We (3) have described a patient with sinus bradycardia and neuroleptic-induced akathisia who was treated with pindolol, a β blocker with intrinsic sympathomimetic activity; pindolol successfully treated the akathisia and, possibly because of the sympathomimetic activity, did not further lower the patient's heart rate. We now report further open data on the efficacy of pindolol in nine patients with neuroleptic-induced akathisia.

This investigation was approved by the subcommittee on human subjects at a Veterans Administration medical center, and all patients gave written informed consent to participate. Neuroleptics and all other medications were held constant throughout the study. Seven patients were diagnosed as having chronic schizophrenia, one patient had an organic psychosis, and another had schizoaffective disorder. Six subjects were inpatients, and the remaining three were outpatients. The patients ranged in age from 28 to 57 years (mean±SD=37.7±8.0 years). Patients were rated for subjective and objective akathisia at baseline and several times during treatment. Subjective akathisia was assessed by having the patient mark a 100-mm line corresponding to perceived restlessness; objective akathisia was rated by the akathisia item on the Hillside/Long Island Jewish Hospital modification of the Simpson/Angus EPS Scale (2).

All nine patients were treated first with pindolol, 5 mg/ day, for 2-4 days (mean ±SD=3.3±0.9 days). Mean ±SD scores for akathisia at baseline and on the last day of treatment with pindolol were as follows: subjective score at baseline= $70.0\pm22.4$  and after treatment= $41.1\pm35.9$ ; objective score at baseline=2.9±0.9 and after treatment=1.9± 1.3. Three subjects had a nearly complete response to the medication, and one subject had a substantial reduction of both subjective and objective akathisia. The remaining five subjects did not substantially improve on the pindolol regimen (two patients showed slight improvement, another was unchanged, and two were slightly worse). These five patients were then treated with propranolol, 40-80 mg/day (mean±  $SD = 72.0 \pm 11.0 \text{ mg/day}$ , for 2-8 days (mean  $\pm SD = 3.8 \pm 2.5$ days). Four of the five patients had a further response to propranolol; the remaining patient's akathisia scores were substantially the same with propranolol and pindolol.

Pindolol did improve mean subjective and objective measures of akathisia; however, the improvement was not as great as in previous studies with propranolol (1, 2). Four of the five patients who had limited responses to pindolol obtained further improvement with propranolol. This differential effect is not likely to have been due to differences in the relative doses of these medications, because the dose of pindolol was the minimum proposed antihypertensive dose and was, if anything, relatively higher than the doses of propranolol we used (mean dose=72.0 mg/day; minimum recommended antihypertensive dose=80 mg/day).

Pindolol and propranolol differ in that 1) pindolol, but not propranolol, has the partial agonist property of intrinsic sympathomimetic activity, and 2) although both drugs are relatively lipophilic, pindolol is not as lipophilic as propranolol (4) and therefore may have a lower acute penetration of the blood-brain barrier.

These preliminary data indicate that pindolol can be an effective treatment for patients with neuroleptic-induced akathisia. It may in fact be the preferred treatment if  $\beta$  blockers must be used in patients with bradycardia.

#### REFERENCES

- Lipinski JF Jr, Zubenko GS, Cohen BM, et al: Propranolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry 1984; 141:412–415
- Adler L, Angrist B, Peselow E, et al: A controlled assessment of propranolol in the treatment of neuroleptic-induced akathisia. Br J Psychiatry 1986; 149:42-45
- Reiter S, Adler L, Erle S, et al: Neuroleptic-induced akathisia treated with pindolol. Am J Psychiatry 1987; 144:383–384
- Frishman W: Beta-adrenergic antagonists: new drugs and new indications. N Engl J Med 1981; 305:500-506

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### Possible Toxic Interaction Between Cyproheptadine and Phenelzine

SIR: It has been reported that cyproheptadine safely alleviates anorgasmia associated with tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants (1–3). Here I describe a probable toxic interaction between cyproheptadine and phenelzine, an MAOI.

Ms. A, a 30-year-old woman with bulimia and recurrent unipolar depression, had medicated herself with amphetamine in the past without toxicity but otherwise abused no drugs or alcohol. There was no family history of affective disorder. She responded well to treatment with phenelzine, 30 mg/day, although she had side effects of anorgasmia, insomnia, and orthostatic hypotension. After 4 months, cyproheptadine, 2 mg at bedtime, was successfully added to her regimen to relieve the anorgasmia. After 2 months of taking the combination (a total of 6 months taking phenelzine), she became unusually irritable for several days. She then abruptly developed visual hallucinations of animals and miniature people and became very frightened, although she knew them to be unreal. Her medications, which she had taken reliably, were stopped, and the hallucinations cleared over 48 hours. She had no increase in insomnia but became more frightened, irritable, and belligerent, refusing medical attention until her family called police, who took her to an emergency room. The results of a physical examination were unremarkable; her mental status examination noted angry affect but no delusions, further hallucinations, or cognitive deficits. She was sedated with haloperidol, 2.5 mg, hospitalized for several days for observation, and released in a normal state. Her depressive and bulimic symptoms recurred 1 month later and responded for 6 months to lithium, which was stopped because of hair loss. She then took desipramine for 12 months, with no recurrence of hallucinations or agitation.

This case illustrates a probable organic hallucinosis induced by the combination of cyproheptadine and phenelzine. Neither drug alone in these low doses has been reported to cause this syndrome in other healthy patients. While phenelzine alone is known to cause mania in certain patients, Ms. A did not have characteristic symptoms of mania other than irritability. Visual hallucinosis in particular is more often the presentation of an organically induced syndrome than of affective illness. There was no evidence of alcohol withdrawal, which can produce similar symptoms, or other drug ingestion. It is possible that there was some unusual interaction with food which caused the delirium, although the patient lacked a known history of dietary noncompliance and did not describe typical symptoms of a hypertensive crisis, the most common problem related to food.

The interaction could be explained in two ways. First, cyproheptadine is a potent blocker of serotonin and H<sub>I</sub> histamine receptors and a weak anticholinergic agent (4). Some interaction with phenelzine's effects on neurotransmitter function may have been toxic. Second, visual hallucinations have been described as a component of phenelzine withdrawal (5). Cyproheptadine may have competitively reversed some activity of phenelzine, accounting for its ability to relieve a side effect but provoking a withdrawal syndrome. It would be hard to explain a 2-month delay in this mechanism, however.

In summary, it would be prudent to watch for adverse CNS side effects on the combination of cyproheptadine and phenelzine.

#### REFERENCES

- Sovner R: Treatment of tricyclic antidepressant-induced orgasmic inhibition with cyproheptadine (letter). J Clin Psychopharmacol 1984; 4:16
- Decastro RM: Reversal of MAOI-induced anorgasmia with cyproheptadine (letter). Am J Psychiatry 1985; 142:783

 Riley AJ, Riley EJ: Cyproheptadine and antidepressant induced anorgasmia (letter). Br J Psychiatry 1986; 142:217–218

 Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1985, pp 634–635
 Liskin B, Roose SP, Walsh BT, et al: Acute psychosis following

 Liskin B, Roose SP, Walsh BT, et al: Acute psychosis following phenelzine discontinuation. J Clin Psychopharmacol 1985; 5: 46-47

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### Heroin Addiction Treated by Atropine Coma

SIR: We would like to present the case of a patient with heroin addiction whom we treated with atropine coma.

Ms. A, born in 1962, was first treated in our department in 1982 for severe heroin addiction. She had been taking heroin since 1978. In 1981, at the insistence of her parents, she had begun treatment. Six courses of pharmacological treatment in mental hospitals had produced no results, and a course of treatment in a rehabilitation center had also been unsuccessful.

On admittance to our hospital, Ms. A was emaciated, euphoric, and garrulous, with hazy consciousness. Her forearms had numerous puncture marks from intravenous injections. She admitted that she had taken a heavy dose of heroin just before reporting to our department.

On her second day of hospitalization, marked withdrawal symptoms appeared: hypotension, tachycardia, nausea, vomiting, pains in the abdomen and joints, hand tremor, excessive fear, and anxiety. After 1 week of pharmacological treatment, we observed an alleviation of these symptoms.

After 1 month's treatment, Ms. A's somatic state was considered satisfactory. Her symptoms of physical drug dependence had disappeared, but a marked mental dependence remained. Bearing in mind the similarity of many elements of mental drug dependence to her obsessive thoughts, we decided to try atropine coma treatment. This form of treatment in obsessive-compulsive disorder was recommended by Forrer (1, 2).

The atropine coma was induced twice a week. Atropine sulfate was administered intramuscularly in doses of 150 mg (the first coma) to 260 mg (the last coma). We used a 10% solution of the atropine sulfate (from 1.5 cm³ to 2.6 cm³). The patient was aroused from the coma after 3 hours with an intravenous injection of neostigmine in amounts corresponding to the atropine doses (from 20 mg to 30 mg). This coma treatment was applied eight times; Ms. A tolerated it well. After the third coma, the intensity and frequency of the obsessive thoughts of taking drugs had diminished. After the final coma, such thoughts were of a very low intensity. After being discharged from the hospital, the patient came of her own free will for an atropine coma maintenance treatment once a month. She had three such treatments.

Ms. A reported to us again 3 years later. She was admitted to the hospital in a heroin-narcotized state. She had taken her first dose of heroin, after a period of abstinence, only 3 weeks before the present hospitalization. She stated that she had completely abstained from drugs for nearly 3 years; this was confirmed by her mother. The patient stressed the efficacy of the atropine coma treatment she had received earlier.

The second period of hospitalization lasted only 8 days. No withdrawal symptoms were observed. The very slight mental drug dependence we observed disappeared after small doses of doxepin. On discharge, Ms. A had a strong motivation to resume the studies she had begun during her 3-year period of abstinence.

Although the result of atropine coma therapy in this patient may represent merely a placebo response, her improvement was striking and warrants further clinical trials of this treatment.

### REFERENCES

- Forrer GR: Atropine toxicity in the treatment of mental disease. Am J Psychiatry 1951; 108:107-112
- Bilikiewicz T, Bilikiewicz A, Dolmierski R, et al: Das Atropinkoma als psychiatrische Behandlungsmethode. Psychiatr Neurol Med Psychol (Leipz) 1963; 12:449–455

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### Reversal by Bethanechol of Imipramine-Induced Ejaculatory Dysfunction

SIR: Case reports and clinical studies have suggested that most of the antidepressants in current use may be associated with impairment of the ejaculatory reflex. It has been suggested that these effects may be secondary to adrenergic, serotonergic, or anticholinergic actions of these drugs, although the precise mechanisms in the various dysfunctions remain unclear. Erectile dysfunction associated with tranylcypromine and isocarboxazid and amoxapine-induced anorgasmia can be reversed by the cholinomimetic agent bethanechol, although this treatment has been reported to be ineffective in restoring imipramine-induced anorgasmia (1). To my knowledge, the following is the first report of the reversal of imipramine-induced anorgasmia with bethanechol.

On initial evaluation, Mr. A, a 37-year-old married man who had a history of recurrent major depressive episodes with paranoid features, complained of failure to ejaculate and prolongation of erections for 30 minutes after cessation of sexual activity. His medication at that time included trifluoperazine, 5 mg h.s., benztropine, 2 mg b.i.d., and trazodone, 250 mg h.s. It was suspected that his prolonged erections might be prodromal to priapism. Therefore, trazodone was immediately discontinued and desipramine begun. The desipramine had to be discontinued after 2 days, however, because of generalized urticaria; imipramine, 250 mg/day, was begun. The patient's prolonged erections subsided with the change in pharmacotherapy, but his failure to ejaculate persisted. Subsequent discontinuation of trifluoperazine and benztropine did not relieve his ejaculatory problem. However, taking 10 mg of bethanechol 30 minutes before sexual activity restored the ejaculatory response. To date, Mr. A has remained on this therapeutic regimen for 6 months, and attempts to discontinue bethanechol have consistently led to the return of ejaculatory difficulties.

The role of cholinergic mechanisms in erection and ejaculation are obscure, and the mechanism whereby bethanechol

might restore ejaculatory function is unclear. Studies in normal subjects have reported no effects of methylatropine, atropine, or bethanechol on sexual arousal or orgasm (2, 3). All of the antidepressants that have been reported to cause ejaculatory impairment (including tricyclics and monoamine oxidase inhibitors) seem to enhance adrenergic function through inhibiting inactivation of norepinephrine (4, 5). It is likely that normal ejaculatory function requires a balance of adrenergic and cholinergic systems and that bethanechol helps to restore a balance which may be disrupted by many antidepressant medications.

#### REFERENCES

- Segraves RT, Madsen R, Carter CS, et al: Erectile dysfunction associated with pharmacological agents, in Diagnosis and Treatment of Erectile Disturbances. Edited by Segraves RT, Schoenberg HW. New York, Plenum, 1985
- Wagner G, Levin RJ: Effect of atropine and methylatropine on human vaginal blood flow, sexual arousal and climax. Acta Pharmacol Toxicol (Copenh) 1980; 46:321–325
- Riley AJ, Riley EJ: Cholinergic and adrenergic control of human sexual responses, in Psychopharmacology and Sexual Disorders. Edited by Wheatley D. Oxford, Oxford University Press, 1983
- Sorscher SM, Dilsaver SC: Antidepressant-induced sexual dysfunction in men: due to cholinergic blockade? J Clin Psychopharmacol 1986; 6:53-55
- Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. Edited by Gilman AG, Goodman LS, Rall TW, et al. New York, Macmillan, 1985

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### Murphy's Law of Psychopharmacology

SIR: The antidepressant medication that makes the patient feel like having sex again will cause anorgasmia.

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### AIDS Delusions: A Symptom of Our Times

SIR: The fear of AIDS contamination is now spreading from the homosexual population to the heterosexual population, and no one feels completely safe from the onslaught of this impending epidemic. Already clinicians have begun to see the incorporation of society's fears about AIDS into the symptom complex of patients presenting with psychiatric illnesses. Various authors have reported patients with anxiety states (1), conversion disorders (1), depression (2), and even factitious illnesses (3) in which fear of AIDS contamination was a prominent feature.

We recently saw four patients who expressed the delusional conviction that they had contracted AIDS. All of these patients were at low risk for AIDS, and all had normal findings on physical examination. Two of the patients had major depression with psychotic features, one patient had schizoaffective disorder, and one patient had paranoid schizophrenia. In two cases (one patient with major depression and the patient with schizoaffective disorder), neurovegetative symptoms that were present were misconstrued by the patients as further evidence of AIDS, a phenomenon previ-

ously reported by Miller et al. (2). In each case, the somatic delusion about AIDS resolved with appropriate therapy for the underlying disorder.

Society's preoccupations or concerns have historically been reflected in the content of patients' delusions. Fear of AIDS contamination is a symptom of our times; as long as the public frenzy concerning AIDS persists, we can expect more patients to incorporate AIDS delusions into their presenting symptom complex. Our experience with these four patients underscores the diagnostic heterogeneity inherent in this delusional belief and suggests that clinicians must keep differential diagnosis foremost in mind when such a presentation is encountered.

#### REFERENCES

- O'Brien G, Hassanyeh F: AIDS-panic: AIDS-induced psychogenic states (letter). Br J Psychiatry 1985; 147:91
- Miller D, Green J, Farmer R, et al: A "pseudo-AIDS" syndrome following from fear of AIDS. Br J Psychiatry 1985; 146:550– 551
- 3. Miller F, Weiden P, Sacks M, et al: Two cases of factitious acquired immune deficiency syndrome (letter). Am J Psychiatry 1986; 143:1483

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### Informed Consent for Neuroleptics and Other Psychotropic Agents

SIR: As psychiatrists on a multidisciplinary departmental committee to evaluate consent forms for psychotropic medication, we struggled with the advisability of obtaining written informed consent before initiating treatment with neuroleptics and other psychotropic agents. To assess practices at other institutions, our committee sent requests to 62 psychiatry programs in the United States and Canada for information regarding their policies on written informed consent. Programs were selected from the *Directory of Psychiatry Residency Training Programs* (1) and were chosen to provide a diverse geographic sampling. We thought your readers would be interested in the results.

Thirty-two programs responded. Twenty-four of these programs do not require written signed consent for patients receiving neuroleptic medication. Two of the programs have a policy requiring written consent only for individuals receiving neuroleptics beyond a 3-month period. Six of the programs routinely require signed consent for all patients receiving neuroleptics. Four of these six programs are in California and are required by state law to obtain written informed consent for psychotropic medication. Four programs obtain written informed consent in special cases, such as administering lithium to women during their childbearing years, use of combined monoamine oxidase inhibitor/tricy-clic antidepressant, and antiandrogen medication. One program requires written informed consent for neuroleptics only if tardive dyskinesia is present.

Of the 24 programs that do not require signed consent, 10 require that informed consent for neuroleptics be documented in the medical chart. Two programs mentioned routine use of the Abnormal Involuntary Movement Scale for patients receiving long-term neuroleptic medication. Five programs sent copies of printed material that is routinely

given to patients who are receiving psychotropic medication.

Taking into account this information, our committee advised against the routine use of written informed consent for patients receiving psychotropic medication. We believe this is in keeping with a demonstrated national standard and with the recommendations of the 1980 American Psychiatric Association task force report on tardive dyskinesia (2). We also suggested following the task force recommendation that informed consent for neuroleptic medication be documented in the patient's record.

#### REFERENCES

- American Association of Directors of Psychiatric Residency Training: Directory of Psychiatry Residency Training Programs, 3rd ed. Edited by Robinowitz C, Kay J, Taintor Z. Washington, DC, American Psychiatric Press, 1986
- Task Force on Late Neurological Effects of Antipsychotic Drugs: Tardive dyskinesia: summary of a task force report of the American Psychiatric Association. Am J Psychiatry 1980; 137:1163–1172

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### Compact Camcorders for Teaching Psychiatric Interviewing

SIR: Recent advances in home video technology have made the use of video equipment to teach psychiatric interviewing both practical and affordable. Older video equipment was bulky, expensive, and complicated, requiring bright lights and some expertise to operate. Unless the equipment was maintained and operated by trained technicians in specially equipped studios, its routine use was difficult.

Compact camcorders have changed all this. The compact camcorder combines a tiny video cassette recorder and a video camera into a single unit. It uses video cassettes only slightly larger than audio cassettes. The whole unit weighs about 3 lb. and is easily held and operated with one hand. The controls are simple, and nearly everything is automatic. Ordinary office lighting works well, and the picture and sound quality are excellent. To review a tape the user plugs the camcorder into any television set. No other video cassette recorder is needed.

I have been using a compact camcorder and portable color television set in my office on a general psychiatry ward to teach psychiatric interviewing and examination on an individual basis to residents and medical students. The procedure is simple. I obtain consent, rearrange office seating, set the camera on my desk, and start recording. Afterward, I review the tape with the resident, pausing and rewinding as needed, to point out good and bad techniques and to offer alternative responses. I review the patient's mental status in detail and find that it is much easier to teach residents to recognize specific disturbances in affect and thinking with this procedure than by reviewing our memories of the interview. Finally, I discuss with the residents how their emotional responses to the patient may have affected the interview from moment to moment. The residents' reports of how they felt, combined with the video record of their nonverbal responses, are especially helpful in this regard.

Patients have consented readily and tolerated the procedure well. Residents and students are initially apprehensive

but afterward report increased confidence, both because their technique usually looks better than they expected and because they feel that their repertoire of responses and their observational skills have increased.

Videotaping to teach psychiatric interviewing is not new (1). What is new is that compact camcorders make it easy and enjoyable.

#### REFERENCE

1. Berger MM (ed): Videotape Techniques in Psychiatric Training and Treatment. New York, Brunner/Mazel, 1978

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### Nicotine and Panic Attacks

SIR: Brodsky (April 1985 issue of the *Journal*, p. 524) reported that several of his patients attenuated the symptoms of panic disorder by smoking. Hughes (February 1986 issue, p. 271) then proposed that nicotine gum might abate panic attacks. Maany et al. (February 1987 issue, p. 255) concluded that nicotine could have at most a limited role in the treatment of panic disorder, since tolerance rapidly develops to its sedative effects. I would like to offer a synthesis that takes these various points into account.

First, data indicate that panic disorder is related to dysregulation of noradrenergic mechanisms (1-3). For instance, the  $\alpha_2$  antagonist yohimbine can precipitate panic anxiety (1), and treatments that down-regulate  $\alpha_2$  receptors and decrease norepinephrine turnover (3) are effective antipanic agents. Nicotine can actually mobilize adrenergic mechanisms (4, 5). First, nicotine can cause the release of norepinephrine and epinephrine from sympathetic ganglia and the adrenal medulla. This can result in increased heart rate and blood pressure. Further, nicotine can paralyze the parasympathetic cardiac ganglia. Nicotine also excites respiration by activation of the carotid and aortic bodies. Activation of the aortic and carotid body chemoreceptors results in reflex vasoconstriction, tachycardia, and increased blood pressure. The drug also activates parasympathetic ganglia and cholinergic nerve endings regulating the tone and motor activity of the bowel (4). Finally, nicotine promotes the release of norepinephrine in the hypothalamus (5). Thus, at high concentrations nicotine can produce physiological effects characteristic of panic attacks.

However, nicotine can have a calming or sedating effect on humans. Perhaps nicotine attenuates the severity of panic anxiety by preventing the development of a nicotine withdrawal syndrome. Abrupt cessation of or reduction in the use of tobacco can be followed within 24 hours by craving, irritability, anxiety, difficulty concentrating, headache, restlessness, and gastrointestinal distress; many of these are symptoms of panic. Thus, one must consider the possibility that the amelioration of panic anxiety by the recent use of tobacco is related more to the attenuation of a nicotine withdrawal syndrome than to an intrinsic property of nicotine that renders it an antipanic agent.

### REFERENCES

 Charney DS, Heninger GR, Breier A: Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 1984; 41:751-763

- Charney DS, Heninger GR: Abnormal regulation of noradrenergic function in panic disorders. Arch Gen Psychiatry 1986; 43:1042–1054
- Charney DS, Heninger GR: Noradrenergic function and the mechanism of action of antianxiety treatment: effect of longterm imipramine treatment. Arch Gen Psychiatry 1985; 42: 473-481
- Taylor P: Ganglionic stimulating and blocking agents, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. Edited by Gilman AG, Goodman LS, Rall TW, et al. New York, Macmillan, 1985, pp 217-218
- New York, Macmillan, 1985, pp 217–218
  5. Westfall TC: Effects of acetylcholine on the release of [<sup>3</sup>H]norepinephrine by nicotine and potassium chloride in rat brain slices, in Frontiers of Catecholamine Research. Edited by Usdin E, Snyder SH. New York, Pergamon Press, 1973

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### Misuse and Abuse of Benzodiazepines

SIR: The study by Drs. Garvey and Tollefson (1) suggests that with proper precautions, benzodiazepines can be administered under the direction of psychiatrists to patients with primary anxiety and major depressive disorders. If we accept these data as valid and representative, what remains at issue is the abuse/misuse potential of benzodiazepines in a multitude of other conditions for which they are in fact used. Moreover, a better evaluation of the long-term therapeutic use of these agents through systematic controlled clinical research is needed.

Considerable numbers of people with and without physical disorders take benzodiazepines chronically for insomnia and anxiety, but data demonstrating the long-term safety and efficacy of these agents are inconclusive or nonexistent (2). In their study Drs. Garvey and Tollefson intentionally excluded from consideration any patient with a history of primary drug and alcohol abuse or dependence, yet, one would intuit—and several authors have indicated—that at least some types of drug abusers are likely to abuse or misuse benzodiazepines (3). One can speculate on how much misuse and abuse of benzodiazepines occur in anxious patients suffering from somatoform disorders, physical illnesses affected by psychological factors, or DSM-III axis II personality disorders, e.g., borderline personality disorder (for which impulsivity relating to substance use is an inclusion criterion) or the "anxious cluster" (4).

Misuse and abuse of the benzodiazepines by patients may be compounded by iatrogenic misuse. It is estimated that up to 70% of prescriptions for diazepam are written by general and family practitioners, internists, and surgeons (5). In all likelihood, these physicians are treating a heterogeneous group of patients, only some of whom would meet DSM-III criteria for generalized anxiety or major depressive disorders. Since the indications for prescribing diazepam are not precise, one must question whether these patients conform to the appropriate target populations for benzodiazepine treatment and whether there is a greater tendency for misuse and abuse of these drugs when treatment takes place in a nonpsychiatric context.

Another salient issue is the length of time during which a patient should be treated with benzodiazepines, assuming that the initial indication for treatment is valid. Standards—albeit not rigorously defined—for duration of treatment with neuroleptics, lithium, and antidepressants for schizophrenic, bipolar, and major depressive disorders, respectively, do exist. But for what time interval should standard benzodi-

azepine therapy be used in patients suffering from insomnia, generalized anxiety or panic, somatoform disorders, or physical illnesses with psychological components? When this time period elapses and a patient with minimal improvement continues to take prescribed medication, is this not iatrogenic misuse? Iatrogenic misuse can be minimized by a greater commitment of physician time and enhanced knowledge about the risk of habituation, psychological impairment, and withdrawal after use of benzodiazepines.

In summary, the use, misuse, and abuse of benzodiazepines need further study in terms of the appropriateness of the diagnostic categories that routinely receive them for treatment and the context in which, and the length of time during which, treatment is dispensed. Drs. Garvey and Tollefson have made a nice start.

#### REFERENCES

- Garvey MJ, Tollefson GD: Prevalence of misuse of prescribed benzodiazepines in patients with primary anxiety disorder or major depression. Am J Psychiatry 1986; 143:1601–1603
- Baldessarini RJ: Chemotherapy in Psychiatry. Cambridge, Harvard University Press, 1985
- Ciccone PE, O'Brien CP, Khatami M: Psychotropic agents in opiate addiction: a brief review. Int J Addict 1980; 15:499-513
- O'Brien CP, Woody GE: Sedative-hypnotics and antianxiety agents, in Psychiatry Update: The American Psychiatric Association Annual Review, vol V. Edited by Hales RE, Frances AJ. Washington, DC, American Psychiatric Press, 1986
- Hasday JD, Karch FE: Benzodiazepine prescribing in a family medicine center. JAMA 1981; 246:1321–1325

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### Dr. Garvey and Dr. Tollefson Reply

SIR: Dr. Ciccone has raised many interesting points. We agree that benzodiazepines may be prescribed for certain conditions for which there are not a great many data to support their use. We also agree that drug abusers, if given the chance, will abuse benzodiazepines (1). However, we disagree with the widely held notion that benzodiazepines carry a significant risk for abuse for most individuals (2). In fact, many of the available data relating to this topic suggest the opposite. Marks, in a review of the pre-1978 literature (3), found that published articles did not suggest that benzodiazepines caused abuse problems for the overwhelming number of patients who used them. On the basis of both published and unpublished but recorded cases, Marks estimated the prevalence of benzodiazepine dependence/abuse in the United Kingdom to be 10.7 patients per one million months of benzodiazepine use. This estimate is probably less than the true prevalence of abuse/dependence, but doubling or tripling the estimate still suggests that the number of patients who have problems with benzodiazepines is far smaller than believed by most physicians. Published largescale surveys (reviewed by Marks) that involved more than 20,000 patients using benzodiazepines revealed that three patients had problems.

Dr. Ciccone suggests the physicians would be less likely to misprescribe benzodiazepines if there were a "greater commitment of physician time and enhanced knowledge about the risk of habituation, psychological impairment, and withdrawal after use of benzodiazepines." Contrary to the notion that physicians are unaware of the potential dangers of benzodiazepines, it is our opinion that both physicians and

the general public are very aware of such problems, perhaps too much so (2). In our group of 71 patients, between one-third and one-half were reluctant to start taking benzodiazepines because of concerns about becoming addicted or some similar problem. Several of these patients stopped their medications prematurely because of fear of addiction. We also saw many examples of patients who had previously been successfully treated with benzodiazepines whose drugs were discontinued within weeks of the beginning of drug therapy because the treating clinician feared the patient would get "hooked." Hollister et al. (4) studied the long-term use of diazepam in 108 neurosurgical patients and found no evidence of dependence or abuse. Rickels et al. (5), in a study of 180 chronically anxious patients treated with benzodiazepines, similarly found no evidence of abuse or dependence. However, Rickels et al. did note that a sizable minority had some evidence of withdrawal symptoms when they were shifted abruptly to placebo, although for most of these patients such symptoms were mild. A gradual tapering of benzodiazepines reduces withdrawal symptoms.

Benzodiazepines are not risk-free drugs. However, the lack of knowledge and understanding about these risks has led to an unnecessarily restrictive use of benzodiazepines by many physicians.

### REFERENCES

- Woody GE, Mintz J, O'Hare K, et al: Diazepam use by patients in a methadone program—how serious a problem? in Problems of Drug Dependence. Washington, DC, National Academy of Sciences, 1975
- Manheimer DI, Davidson ST, Balter MB, et al: Popular attitudes and beliefs about tranquilizers. Am J Psychiatry 1973; 130:1246–1253
- Marks J: The Benzodiazepines: Use, Overuse, Misuse, Abuse. Lancaster, England, MTP Press, 1985
- Hollister LE, Conley FK, Britt RH, et al: Long-term use of diazepam. JAMA 1981; 246:1568–1570
- 5. Rickels K, Case WG, Downing RW, et al: Long-term diazepam therapy and clinical outcome. JAMA 1983; 250:767-771

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### Nontartrazine Allergy With Desipramine

SIR: Robert Pohl, M.D., and colleagues (1) reported five cases of apparent allergy to tartrazine (FD&C yellow dye number 5) in 170 patients exposed to the dye in antidepressants. These five patients developed urticaria after receiving antidepressant tablets containing tartrazine. Four of these patients were switched to a brand of desipramine without tartrazine and had no recurrence of symptoms. The authors concluded that patients with allergic responses to antidepressants that contain tartrazine are likely to tolerate similar or identical drugs that lack tartrazine.

Mr. A, a 26-year-old man with panic disorder, was treated by me with desipramine tablets (25 mg) that contained tartrazine. After 10 days, while taking 50 mg/day of desipramine, he developed generalized pruritis. Routine laboratory tests revealed a normal CBC and differential, no eosinophils, and a normal chemistry and liver function profile. A history was positive for allergy to codeine, but there was no history of aspirin allergy. The

patient was switched to nortriptyline capsules (25 mg) for 1 week without development of pruritis. After reading the findings of Dr. Pohl and colleagues, I changed Mr. A's medication back to desipramine tablets (50 mg) that did not contain tartrazine. After 5 days, he again developed generalized pruritis. He was then restarted on nortriptyline capsules (25 mg), with resolution of panic attacks and no development of pruritis.

While some patients develop allergic reactions to the tartrazine dye in antidepressants, others may have allergic reactions to other components of the medication or tablet. These may include skin rash, petechiae, urticaria, itching, photosensitization, edema, drug fever, and cross-sensitivity with other tricyclic drugs. This case questions the wisdom of restarting patients who develop allergic reactions while taking antidepressants to similar or identical medications without tartrazine. In light of this case, it seems prudent to switch patients to a chemically unrelated antidepressant and from a tablet to a capsule, or vice versa, in addition to avoiding medications with tartrazine.

#### REFERENCE

1. Pohl R, Balon R, Berchou R, et al: Allergy to tartrazine in antidepressants. Am J Psychiatry 1987; 144:237–238

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### How Long Should Drug Therapy for Depression Be Maintained?

SIR: Drs. Prien and Kupfer (1) have reevaluated the results of their recent National Institute of Mental Health collaborative study of long-term maintenance of drug therapy in affective disorders to address the question of how long antidepressant therapy should be continued. Their suggestion that continuation treatment should be maintained for 16–20 weeks after total remission of symptoms is not in harmony with the often recommended period of 6–12 months. Moreover, Dr. Prien and Dr. Kupfer found a high relapse rate (38%) in the first 8 weeks of follow-up in the patients who received lithium, which was identical to the relapse rate in those who had placebo; patients who received imipramine or a combination of imipramine and lithium relapsed in 5% and 11% of cases, respectively.

This report prompted me to reexamine the results of a previously published study (2) in which my colleagues and I, in the context of a double-blind, placebo-controlled study over the course of a year, assessed the value of lithium as a continuation treatment after recovery brought about by ECT. Outcome was measured in that study by the number of weeks each patient spent in an episode of depression and was determined separately for the first and the second 6 months of the trial. It was found that patients who received lithium spent significantly less time in an episode of illness than those who took placebo in the second 6 months of the trial, indicating the continued vulnerability of depressed patients more than 6 months after their full recovery.

In the reevaluation of these results, outcome was determined by the recurrence of episodes of depression during the trial; an episode (relapse or recurrence) was defined as the occurrence of depressive symptoms that required inpatient treatment. The majority of those who relapsed had received

ECT. Five (25%) of the 20 patients who had received placebo had episodes of depression in the first 15 weeks after recovery, and four (22%) of 18 patients who had received lithium had episodes within this period. Five more patients in the placebo group relapsed between week 13 and week 38 after recovery, giving a total of 10 patients (50%) who had taken placebo who suffered episodes during the trial. Three of the five placebo patients who relapsed early had further relapses during the trial. In the lithium-treated patients, no more episodes of illness occurred, giving a total rate of 22%.

These results would argue for continuation treatment with lithium for a whole year after recovery brought about by ECT. This conclusion may well be qualified by the notion that relapses should be distinguished from recurrences, and it could be assumed that the episodes which occurred earlier in the placebo- and lithium-treated patients were relapses, whereas the episodes which emerged later in the trial, and only in the placebo group, were recurrences of illness. If this notion is accepted notwithstanding the difficulties of distinguishing a recurrence from a relapse, it could be argued that lithium is less effective as a continuation treatment than as a prophylactic therapy.

#### REFERENCES

- Prien RF, Kupfer DJ: Continuation drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry 1986; 143:18-23
- Coppen A, Abou-Saleh MT, Milln P, et al: Lithium continuation therapy following electroconvulsive therapy. Br J Psychiatry 1981; 139:284–287

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### Sleep Reduction: Factor in the Genesis of Mania?

SIR: The suggestion by Thomas A. Wehr, M.D., and his associates that sleep reduction is a "final common pathway" in the genesis of mania (1) is puzzling. Neither the data cited in their paper nor other evidence in the literature, including their own studies (2) and others not cited (3–6), appears to be consistent with such a sweeping, broad hypothesis.

First, they referred to data of their own (2) and of others indicating that deliberate sleep deprivation precipitates mania. Not mentioned in the present paper was their earlier speculation (2) that rapidly cycling manic-depressive patients (those who have four or more episodes of affective illness per year) are more sensitive to the mania-inducing effects of sleep deprivation than the more common bipolar patients who do not cycle rapidly. Their own data were all collected in rapidly cycling patients. Moreover, in their own review of the literature on the effects of deliberate sleep deprivation on depressed bipolar patients (2), they concluded that "less than 15% (probably much less) of the total number of patients studied switched into mania or hypomania after sleep deprivation."

Second, several longitudinal studies (3–6) revealed no major sleep changes preceding mania, with the exception that a small but statistically significant reduction in sleep time (about 1–1.5 hours) was commonly reported on the night before a rapid switch into mania. Sleep loss may accompany the onset of mania in some but not all instances; when it does occur, it is probably part, rather than a cause, of the switch process. In a study of 52 rapid switches into mania (<24 hours), Sitaram et al. (5) found that most (26

switches in 22 patients) occurred between 7:00 a.m. and 3:00 p.m. and were not accompanied by a dramatic loss of sleep either before or during mania. In contrast, the switches associated with major loss of sleep during mania occurred between 3:00 p.m. and 7:00 a.m. No published systematic data are available on sleep during "slow switches" (>24 hours), which were observed in seven of 59 switches into mania in the study by Sitaram et al. (5).

Third, the switch process into mania can apparently occur during sleep itself (3, 5, 6), at a time when the term "sleep reduction" seems inappropriate. In the study by Sitaram et al. (5), 10 patients switched a total of 14 times from depression to mania following an average of 4.8 hours of sleep, as estimated by nurses' bed checks. In a single case study of a rapidly cycling patient who switched five times from depression into mania at night, all-night polygraphic EEG recordings documented sleep up to the apparent onset of mania (3). In a patient with a 48-hour mood cycle who was studied longitudinally for about 2 years, 67.7% of 130 night switches into mania were immediately preceded by sleep (6).

Fourth, no evidence was cited that increased sleep, by pharmacological or other means, dramatically prevents or attenuates mania. Antipsychotic agents or intermediate- and long-acting benzodiazepines may be useful in managing manic patients, but the clinical benefits have not been shown experimentally to result specifically from sleep promotion.

In summary, it remains to be demonstrated whether sleep reduction is a common or uncommon factor in the genesis of mania and, if it is, in which patients. The available evidence, however, does not support the hypothesis that sleep reduction is the final common pathway in most bipolar patients. Dramatic sleep loss does not appear to be necessary or sufficient to trigger mania in most instances and does not invariably precede, accompany, or follow the onset of mania.

### REFERENCES

- Wehr TA, Sack DA, Rosenthal NE: Sleep reduction as a final common pathway in the genesis of mania. Am J Psychiatry 1987; 144:201–204
- Wehr TA, Goodwin FK, Wirz-Justice A, et al: 48-hour sleepwake cycles in manic-depressive illness. Arch Gen Psychiatry 1982; 39:559-565
- 3. Gillin JC, Mazure C, Post RM, et al: An EEG sleep study of a bipolar (manic-depressive) patient with a nocturnal switch process. Biol Psychiatry 1977; 12:711-718
- Post RM, Stoddard FJ, Gillin JC, et al: Slow and rapid alterations in motor activity, sleep, and biochemistry in a cycling manic-depressive patient. Arch Gen Psychiatry 1977; 34:470-477
- Sitaram N, Gillin JC, Bunney WE: Circadian effects on the time of switch, clinical ratings, and sleep in bipolar patients. Acta Psychiatr Scand 1978; 58:267–278
- Sitaram N, Gillin JC, Bunney WE Jr: Circadian variation in the time of "switch" of a patient with 48-hour manic-depressive cycles. Biol Psychiatry 1978; 13:567–574

J. CHRISTIAN GILLIN, M.D. La Jolla, Calif.

### Dr. Wehr and Associates Reply

SIR: Dr. Gillin appears to doubt that "deliberate sleep deprivation precipitates mania." In one of the few studies bearing on this question, however, Dr. Gillin and his collaborators reported that "ratings of elation and talkativeness (activation) increased dramatically" in a group of mostly bipolar patients who responded to sleep deprivation (1); he has proposed that the greater severity of mania after nocturnal switches compared with diurnal switches "could be related to the greater loss of sleep with this type of switch" (2).

The question is not really whether bipolar patients switch into mania after sleep deprivation, but how often. To our knowledge, our 1982 study of sleep deprivation is the only one that used mania ratings specifically to detect mania, and we found that the majority of patients switched into mania or hypomania. Two other groups prospectively measured symptoms commonly associated with mania and found that they markedly increased after sleep deprivation (1, 3). Of the studies we cited, several reported switches into mania or hypomania but did not report the frequency of switches in bipolar patients. Where the frequency can be calculated, it ranges from 0% to 50% (25% to 100% in patients whose depressions improved). However, flaws in the methods of the studies probably led to underreporting of mania and hypomania. 1) None of the studies was designed to measure the prevalence of mania after sleep deprivation. Their focus was on antidepressant effects, and mania was reported incidentally and anecdotally. 2) With this focus, investigators may have failed to detect or report hypomania. 3) Medications were administered in many of the studies. Bipolar patients are often treated with lithium, which may prevent mania after sleep deprivation.

Dr. Gillin states that longitudinal studies show "no major sleep changes preceding mania." In the study by his own group, however, a statistically significant reduction of sleep to 5.0 hours was observed before the switch. As Dr. Gillin has mentioned elsewhere (2), partial sleep deprivation, allowing as much as 4 or 5 hours of sleep, is reported to be as effective an antidepressant as total sleep deprivation. Therefore, it seems plausible that partial sleep deprivation could also precipitate mania, and we did not mean to suggest that the deprivation must be total (or limited to one night) in order to cause a switch.

Dr. Gillin states that "the switch process into mania can apparently occur during sleep itself." It is unclear how the diagnosis of mania can be made when the patient is asleep. In any case this assertion is based almost entirely on a retrospective analysis of records of nurses' 30-minute room checks. With this type of monitoring, the possibility that patients were awake, unobserved, before they switched cannot be excluded. Brief awakenings could be important because, as Dr. Gillin has noted elsewhere, "the results of partial sleep deprivation in the second half of the night suggest that improvement may begin immediately or shortly after awakening" (2).

We don't propose that sleep reduction is the only pathway for the genesis of mania. It is one pathway, however, for which there is experimental evidence, and when mania occurs in a context of sleep disruption, we feel that clinicians should consider a possible causal association. We also believe that it is important for patients and those who are concerned with their welfare to know that the risk of mania is increased after sleep deprivation.

### REFERENCES

- Gerner RH, Post RM, Gillin JC, et al: Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. J Psychiatr Res 1979; 15:21–40
- Gillin JC: The sleep therapies of depression. Prog Neuropsychopharmacol Biol Psychiatry 1983; 7:351–364

3. Kasper S, Moises HW, Beckmann H: Dexamethasone suppression test combined with total sleep deprivation in depressed patients. Psychiatr Clin (Basel) 1983; 16:17-25

THOMAS A. WEHR, M.D. DAVID A. SACK, M.D. NORMAN E. ROSENTHAL, M.D. Beihesda. Md.

### **Psychiatrist-Patient Sexual Contact**

SIR: We read with interest the article by Judith L. Herman, M.D., and associates on psychiatrist-patient sexual contact (1), especially their finding that psychiatrists who had had sexual contact with their patients very often rationalized their behavior. This cognitive distortion or rationalization of inappropriate sexual behavior has been found to be common in men who are involved in other types of inappropriate sexual behavior-e.g., sex with children, rape, or incest (2, 3)—and is used to support their behavior. Incest offenders, for example, often justify their behavior by stating that they love their son or daughter and are helping the child learn about sex in a loving fashion. (Compare this with the psychiatrists cited in the survey who believed in the "therapeutic" value of sexual relations with patients.) Men who are sexually involved with children often minimize the possibility of harm to the child in the same way that most of the psychiatrists in the offender group felt that their behavior was innocuous. Rapists often protest that the victim "knew what she was doing and she liked it," ignoring all evidence to the contrary.

An important part of treatment for sex offenders is the active confrontation of these rationalizations (3). In order to stop sexual acting out, it is imperative that the offender see that his cognitive distortions have contributed to the maintenance of his inappropriate sexual behavior. This is a difficult process (since the offender often does not see the need for treatment to begin with!), and treatment is often not possible unless the offender is motivated to seek it by some aversive consequence (ostracism from his family, criminal prosecution, loss of a job, etc.).

We strongly agree that the American Psychiatric Association should affirm that all sexual contact with patients before and after termination is unethical and that educational programs on the negative effects of such behavior are much needed. However, we feel that these steps alone are not sufficient to curb sexual abuse of patients by their therapists. As noted in the first part of the authors' study (4), only 41% of the offenders voluntarily sought consultation with colleagues because of their sexual involvement with patients. In light of the documented harm that such contact causes patients (4), we strongly advocate treatment for these therapists and their patients; the only way to ensure that these therapists participate in treatment may be to take strong disciplinary measures against them.

### REFERENCES

- 1. Herman JL, Gartrell N, Olarte S, et al: Psychiatrist-patient sexual contact: results of a national survey, II: psychiatrists' attitudes. Am J Psychiatry 1987; 144:164–169
- Abel GG, Becker JV, Cunningham-Rathner J: Complications, consent, and cognitions in sex between children and adults. Int J Law Psychiatry 1984; 7:89–103
- Abel GG, Mittelman MS, Becker JV: Sexual offenders: results of assessment and recommendations for treatment, in Clinical Criminology. Edited by Ben-Aron, Hucker, Webster. Toronto,

#### LETTERS TO THE EDITOR

M & M Graphics, 1985

 Gartrell N, Herman J, Olarte S, et al: Psychiatrist-patient sexual contact: results of a national survey, I: prevalence. Am J Psychiatry 1986; 143:1126-1131

> RICHARD J. KAVOUSSI, M.D. JUDITH V. BECKER, PH.D. New York, N.Y.

### Dr. Herman and Colleagues Reply

SIR: We couldn't agree more. The dynamics of sexual exploitation appear to be much the same whether the perpetrators be pedophiles, rapists, or psychiatrists. In each case, the offender abuses his position of superior power, trust, or authority to obtain sexual gratification from the victim. And in each case, he invokes the same tired rationalizations. We are especially pleased to find that our work is confirmed by Drs. Kavoussi and Becker, investigators in the forefront of sex offender research and treatment whose opinions we greatly respect.

Sexual abuse of power is like an addictive drug. As in the case of other addictions, an active intervention strategy that applies strong, consistent external controls and sanctions and that focuses directly on the problematic attitudes and behavior seems to hold the greatest promise for rehabilitation. Our recommendations for reporting offending psychiatrists are contained in part III of our study (1). A description of model civil and criminal legislation, as well as a model strategy for clinical intervention, will appear in part IV of the study (Gartrell et al., unpublished manuscript). A fuller analysis of the general problem of sexual exploitation will be forthcoming next year (2).

### REFERENCES

 Gartrell N, Herman JL, Olarte S, et al: Reporting practices of psychiatrists who knew of sexual misconduct by colleagues. Am J Orthopsychiatry 1987; 57:287–295

2. Herman JL: Thinking about sex offenders. Signs: Journal of

Women in Culture and Society (in press)

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### Transitional Object Use and Borderline Personality

SIR: We read with interest the paper "Transitional Object Use and Borderline Psychopathology" by Humphrey Morris, M.D., and associates (1). Although we support their attempt to scientifically validate concepts derived from psychodynamic theory, we cannot agree with their conclusion that transitional object use may be a marker for borderline personality disorder. We raise three major objections.

The first objection regards their methodology. We believe that the t test used by the authors to compare the mean transitional relatedness scores of the various diagnostic groups is inappropriate. One of the assumptions underlying the use of the t test is that the measures of the compared groups are normally distributed, which was untrue for most, if not all, of the groups compared. A nonparametric test such as chi-square would be more appropriate.

Our second and major objection is that if transitional object use is to be considered as a marker for borderline persons, it should be able to distinguish borderline persons from normal subjects. When we used the data from the authors' table 1 to calculate a  $2 \times 2$  chi-square analysis comparing the number of borderline and normal subjects using and not using transitional objects, none of the differences between borderline and normal subjects were statistically significant. The authors never reported the results of their comparisons between these groups.

Finally, we believe that insufficient attention was paid to the impact of sex differences between groups on those groups' measures of transitional relatedness. Although the authors reported that analysis of variance confirmed that the five diagnostic groups differed significantly in mean transitional relatedness scores, they failed to report the relative contributions of sex and of diagnosis to the total variance. Furthermore, there were insufficient data in the paper for us to make those calculations ourselves. We believe that those relative contributions should have been stated explicitly.

It appears to us that the authors presented their data selectively so as to confirm a preexisting psychodynamic bias that borderline personality diagnosis is correlated with transitional object use.

#### REFERENCE

 Morris H, Gunderson JG, Zanarini MC: Transitional object use and borderline psychopathology. Am J Psychiatry 1986; 143: 1534–1538

> LAWRENCE W. ADLER, M.D. Baltimore, Md. HIRAM E. ZENGOTITA, M.D. Houston, Tex.

SIR: Humphrey Morris, M.D., and his colleagues reported significant correlations between 1) childhood and adult use of transitional objects and 2) scores on the Diagnostic Interview for Borderline Patients. Use of transitional objects was mostly highly correlated (p values<.01) with four symptoms: regression in hospital (or psychotherapy), staff splitting (or other countertransference problems), depersonalization, and self-mutilation. All four of these symptoms are characteristic of patients with dissociative disorders, a set of diagnoses not specified as having been ruled out in the study cohort. Previous studies have documented overlap between dissociative disorders and borderline personality disorder; 70% of patients with multiple personality disorder meet criteria for borderline personality disorder (1).

If some of the borderline patients in this study had coexisting dissociative disorders, this could explain the concentration in this group of transitional object use and the highly correlated four symptoms. 1) Regression: patients with multiple personality disorder often have a child alter who uses transitional objects and who "comes out" when they are hospitalized, producing regressed behaviors (2). 2) Staff splitting: patients with multiple personality disorder also routinely stress and split staff members, who may have basic conflicts about whether the diagnosis exists. 3) Depersonalization: itself a dissociative disorder, it is also a dissociative symptom found in multiple personality disorder, amnesias, fugues, and atypical syndromes. 4) Self-mutilation: two surveys of 170 multiple personality disorder patients indicated that more than 68% had attempted suicide at least once (3). Like multiple personality patients, the majority of patients with borderline personality disorder have a history of physical and sexual abuse in childhood (2); such histories have been correlated with later violence toward self and others within several diagnostic groups (4). Experiences of child abuse and neglect have also been linked with the development of excessive attachments to nonhuman aspects of the environment, including transitional objects (5).

A case example illustrates the dissociative symptoms underlying what was initially assessed as transitional object use in a borderline patient.

Mr. A, a 28-year-old-man, was terminated from a day hospital because he insisted on bringing his backpack to every session. The backpack contained a stuffed animal, diapers, a pacifier, and a bottle. Further investigation revealed that these paraphernalia "belonged" to a named 2-year-old personality fragment and were used in a paraphilia pursued by another named fragment; an angry fragment had alienated the staff in the struggle over the backpack; and it was the depressed core personality who threatened suicide when this struggle was lost. In dealing with this patient's problems it has been helpful to link his ego fragmentation to his previous childhood abuse and to help him escape the intrafamilial sexual abuse that was still going on at the time he entered treatment.

### REFERENCES

- Horevitz RP, Braun BG: Are multiple personalities borderline? Psychiatr Clin North Am 1984; 7:69–87
- Herman J: Traumatic antecedents of borderline personality disorder, in Psychological Trauma. Edited by van der Kolk B. Washington, DC, American Psychiatric Press, 1987
- Bliss EL: Multiple Personality, Allied Disorders and Hypnosis. New York, Oxford University Press, 1986, p 154
- Yesavage JA, Widrow L: Early parental discipline and adult self-destructive acts. J Nerv Ment Dis 1985; 173:74–77
- Searles H: The Non-human Environment in Normal Development and Schizophrenia. New York, International Universities Press, 1960

JEAN GOODWIN, M.D., M.P.H. Milwaukee, Wis.

### Dr. Morris and Associates Reply

SIR: The objections raised by Drs. Adler and Zengotita concern what we take to be the central, and unresolved, question in our study: whether transitional object use could serve as a developmental and psychodynamic marker for borderline persons.

With regard to methodology, we felt that the data called for analysis both by t test and by chi-square. As we reported, we did perform both and obtained substantially the same results with each.

That borderline and normal subjects did not differ significantly on our measures of transitional object use certainly suggests that the *absence* of transitional object use in the nonborderline axis II group may have been our most significant finding. As we stated, we believe that these and other distinctions (e.g., between transitional objects and fetishistic objects) require more definitive research strategies. Other important cases in point would be the determination of the relative contributions of sex and diagnosis to transitional relatedness scores.

We agree with Drs. Adler and Zengotita that our results

are tentative; we claim no more. Our intent in this study was to determine in a preliminary way whether the often takenfor-granted association between borderline diagnosis and transitional relatedness had empirical support.

Dr. Goodwin raises the possibility that some of the borderline patients in our study had coexisting, undiagnosed dissociative disorders. We think this quite unlikely, given that none of our subjects received such a diagnosis at discharge despite the fact that McLean Hospital clinicians are aware of the criteria for multiple personality disorder and other dissociative disorders.

HUMPHREY MORRIS, M.D. JOHN G. GUNDERSON, M.D. MARY C. ZANARINI, ED.M. Belmont, Mass.

### DST Status Not Predicted by Serum Sodium Levels

SIR: In their article on prediction of postdexamethasone cortisol levels by serum sodium levels in patients with major depression (1), Gary Tollefson, M.D., Ph.D., and associates reported that patients with low sodium levels (<140 mmol/liter) were more likely to be suppressors on the dexamethasone suppression test (DST) and that high sodium levels were associated with DST nonsuppression. The authors suggested that serum sodium levels could have potential screening value for depression and minimize the need for a DST. As part of an ongoing DST study, we routinely screen patients for serum sodium and potassium with the technique described by Dr. Tollefson and his colleagues (ion-selective electrode method) (2). Retrospective analysis of our patient sample did not confirm the association between sodium and postdexamethasone cortisol levels.

We used the same exclusion criteria as Dr. Tollefson. Twenty-six patients (18 women and eight men) with major depression had 8:00 a.m. electrolyte determinations before a DST. The mean age of the patients was 43 years; 18 were drug free except for nighttime sedation. Blood samples for determining plasma cortisol were collected at 4:00 p.m. before administration of dexamethasone (1 mg at 11:00 p.m.) and at 8:00 a.m. and 4:00 p.m. the next day. Ten of the 26 patients (38%) were nonsuppressors according to a cortisol criterion of 140 nmol/liter (5 µg/dl). The mean±SD sodium (139.5 $\pm$ 2.49 mmol/liter) and potassium (4.09 $\pm$ 0.35 mmol/liter) concentrations were not significantly different between suppressors and nonsuppressors. Further, no significant correlations were observed between pre-DST sodium and post-DST cortisol levels at 8:00 a.m. (r=.21) or 4:00 p.m. (r=.22). There were significant intercorrelations between the pre-DST cortisol and the post-DST cortisol levels  $(8:00 \text{ a.m.}, r=.43; 4:00 \text{ p.m.}, r=.5\hat{5})$  and between the two post-DST cortisol levels (r=.90).

According to a discriminant function analysis, the best predictor of DST nonsuppression was not the sodium levels (Wilks's  $\lambda$ =0.99; n.s.) but the 4:00 p.m. pre-DST cortisol levels (Wilks's  $\lambda$ =0.46; F=26.3, df=1, 23, p<.001). The nonsuppressors had elevated pre-DST cortisol levels (482±175 nmol/liter) compared to the suppressors (218±84 nmol/liter), indicating cortisol hypersecretion. Although in this sample we did not observe a correlation between pre-DST sodium and pre-DST cortisol levels (r=-.15), the correlation between sodium and post-DST cortisol levels reported by Dr. Tollefson and associates could reflect secondary changes produced by chronic hypersecretion of cortisol, as they suggested in their Discussion section.

In conclusion, we find no association between pre-DST sodium and post-DST cortisol concentrations. Therefore, the suggestion by the authors that substituting sodium level measurement for the DST is not justified at this time.

#### REFERENCES

- Tollefson GD, Zander J, Luxenberg M, et al: Prediction of postdexamethasone cortisol levels by serum sodium levels in patients with major depression. Am J Psychiatry 1986; 143:81– 84
- Johnson GF, Hunt G, Kerr K, et al: Dexamethasone suppression test and plasma dexamethasone levels in depressed patients. Psychiatry Res 1984; 13:305-313

GLENN E. HUNT, M.SC. GORDON F. JOHNSON, M.D. Sydney, Australia

### Dr. Tollefson and Associates Reply

SIR: We appreciate the letter by Dr. Johnson and Mr. Hunt. As with most putative relationships, the replication of numerous investigators is welcome. While they do not make specific reference to the diagnosis of major depression in their study, we assume that it was concordant with DSM-III and Research Diagnostic Criteria. Also, were the various factors known to influence the specificity of the outcome of the DST excluded in their patient sample? It is not fully clear what form of statistical analysis was performed by these investigators. In our report a multiple regression analysis was performed, using four different blood chemistries as original predictors. Sodium level was the only measure to achieve significance. A linear regression equation was derived, and through this relationship the 8:00 a.m. sodium level was felt to be predictive of an 11:00 p.m. post-DST cortisol level. Ninety-percent family competence intervals, using the Schefféand Bonferroni algorithms, were then used, after which we used a dichotomous strategy to find the appropriate cutoff. Discriminant analysis was also performed. If Dr. Johnson and Mr. Hunt used only a dichotomous approach, they may have failed to confirm our findings, but they have not excluded a possible relationship within their own sample.

In any event, we welcome this report and any subsequent reports that explore the putative relationship between serum sodium level and elevation of the cortisol level. Symptom severity, depressive subtype, chronicity of therapy, and so forth may all be relevant interstudy variables.

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### Longing for Twinship and Lesbianism

SIR: In discussing twinship needs in their excellent review of Kohut's work (1), the Drs. Baker drew a conclusion about sexuality which ignores the biological influences on behavior that the Bakers themselves reported Kohut "did not adequately address."

The Bakers wrote of a female patient struggling with her need for "sexual contact with a particular [woman] friend." This twinship longing may have been inherently sexual—namely, lesbian—not a sexualization of another longing, as the Bakers suggested. The nature of the patient's parents may well have made it more difficult for the patient to feel twinship with other lesbians and thus resolve her conflict, but it is not likely that the parents' behavior by itself produced her lesbian longings—too many studies these days indicate a strong biological influence on sexual preference (2).

#### REFERENCES

- Baker HS, Baker MN: Heinz Kohut's self psychology: an overview. Am J Psychiatry 1987; 144:1–9
- Marmor J: Overview: the multiple roots of homosexual behavior, in Homosexual Behavior. Edited by Marmor J. New York, Basic Books, 1980

ALLAN H. VALGEMAE, M.D. Washington, D.C.

Reprints of letters to the Editor are not available.

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Dizziness	7.8	3.1	
Nervousness	5.2	4.5	
Lightheadedness	4.9	0.9	
Coordination Disorder/Ataxia Gastrointestinal	4.6	8.0	
Nausea/Vomiting	4.6	3.7	

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

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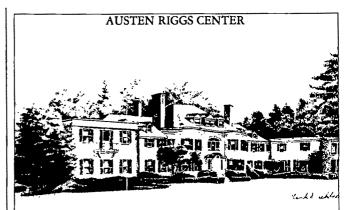
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- 1. Stone AA: Mental Health and Law: A System in Transition. Rockville, Md, NIMH, 1975, pp 102-103
- Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
- 3. Rubinow DR, Post RM, Pickar D, et al: Relationship between

urinary-free cortisol and CSF opiate binding activity in depressed patients and normal volunteers. Psychiatry Research (in press)

4. McNamara JR (ed): Behavioral Approaches to Medicine. New

York, Plenum Press, 1979

 Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

 Smythe GA, Compton PJ, Lazarus L: Serotoninergic control of human growth hormone secretion: the actions of L-dopa and 2bromo-α-ergocyptine. Excerpta Medica International Con-

gress Series 1976; 381:222-235

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# A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.

The incorporation of a triazolo ring to the basic benzodiazepine structure clearly differentiates Xanax from other benzodiazepines.

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# A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.



### XANAX\* Tablets (alprazolam) @

#### CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

### WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

### **PRECAUTIONS**

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with ben-

zodiazepines have been reported. Drug/Laboratory Test Interactions: No consistent pattern for a specific drug or specific test. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic potential or impairment of fertility in rats. Pregnancy: See Warnings. Nonteratogenic Effects: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. Labor and Delivery: No established use. Nursing Mothers: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

### ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/ palpitations, and hypotension. Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor. Cutaneous: Dermatitis/allergy. Other side effects: Nasal congestion, weight gain, and weight loss.

weight gain, and weight loss.
In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia,

dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

### DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S J-6338 January 1987

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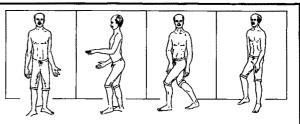
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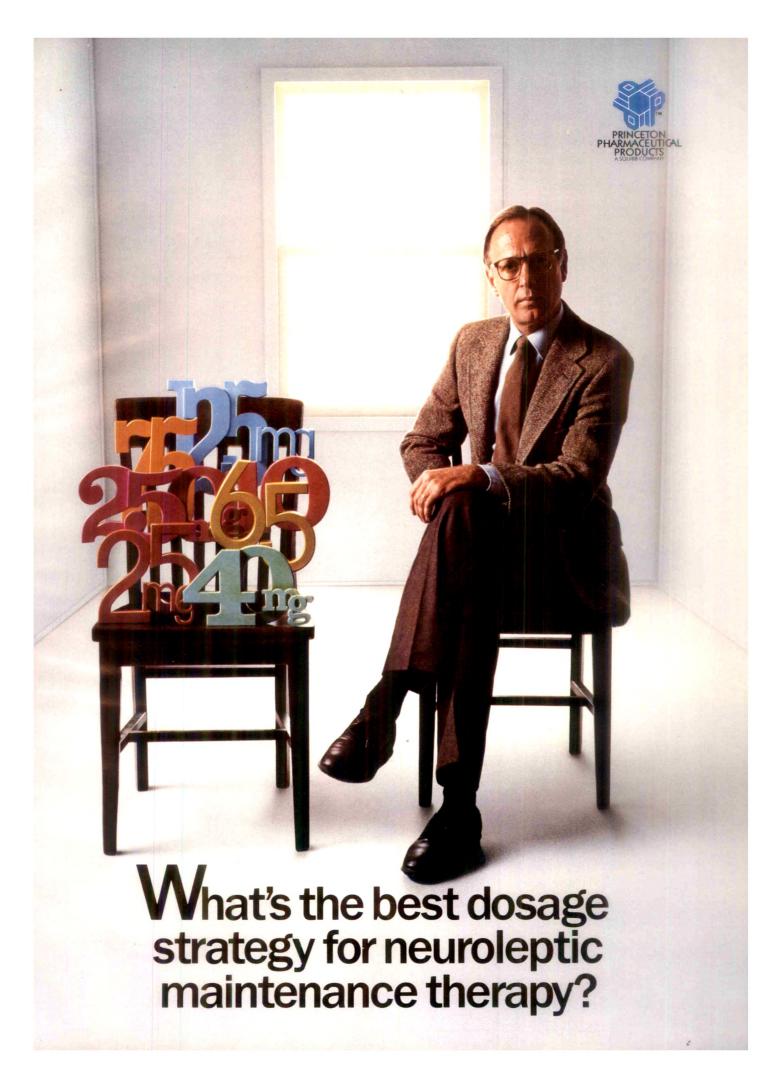
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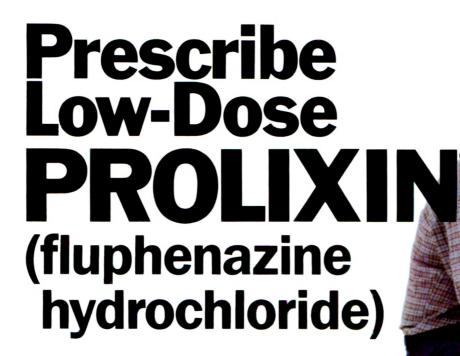


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The maintenance dose should be the minimum amount that maintains therapeutic response and allows the patient to function best. 77\*



Many patients can be maintained on 1 to 5 mg once a day<sup>†</sup>

\*AMA Division of Drugs: AMA drug evaluations, ed 5, Chicago, American Medical Association, 1983, p 219.

†Before prescribing, consult the full prescribing information for recommended dosage and administration.



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- ▶ Fewer anticholinergic effects²
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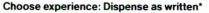
# PROLIXIN® (fluphenazine hydrochloride) ORAL MAINTENANCE

Lowering the dose, lowering dose-related side effects

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<sup>\*</sup> While the risk of extrapyramidal symptoms is increased with high-potency neuroleptics, these symptoms are usually dose-related and can generally be controlled by dosage adjustments.

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#### PROLIXIN® Oral Concentrate (fluphenazine hydrochloride oral solution)

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Fluphenazine Hydrochloride

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PROLIXIN DECANOATE®

Fluphenazine Decanoate Injection

**DESCRIPTION:** Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) provide 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. Prolixin 2.5, 5, and 10 mg tablets contain FD&C Yellow No. 5 (tartrazine). Prolixin Elixir (Fluphenazine Hydrochloride Elixir USP) provides 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. Prolixin Oral Concentrate (Fluphenazine Hydrochloride Oral Solution\*) provides 5 mg fluphenazine hydrochloride per mL, with 14%\* alcohol by volume (exceeds the USP monograph 1.2% limit). Prolixin Injection (Fluphenazine Hydrochloride injection USP) provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. Prolixin Decanoate (Fluphenazine Decanoate Injection) provides 25 mg fluphenazine decanoate per mL in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as preservative.

CONTRAINDICATIONS: In the presence of suspected or established subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur. Fluphenazine Decanoate is not intended for use in children under 12.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irrevers ibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the longterm course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative effective, less harmful treatments are not available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children. Severe adverse reactions, requiring immediate medical attention, may possibly occur.

**Usage In Pregnancy:** Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sen-



#### PROLIXIN® Elixir (fluphenazine hydrochloride elixir USP)

0.5 mg/mL—orange-flavored—in bottles of 473 mL (1 pint) and 60 mL dropper-assembly bottles



#### PROLIXIN® Injection (fluphenazine hydrochloride injection USP)

2.5 mg/mL in multiple-dose vials of 10 mL

sitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine cautiously in patients exposed to extreme heat or phosphorus insecticides, in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine. "Silent pneumonias" are possible. Fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or quardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

ADVERSE REACTIONS: Central Nervous System: Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. One can expect a higher incidence of such reactions with fluphenazine decanoate than with less potent piperazine derivatives or straight-chain phenothiazines. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue protrusion, puffing cheeks, puckering mouth, chewing movements), trunk and
extremities. Severity and degree of impairment vary widely. May become clinically
recognizable either during treatment, dosage reduction, or treatment withdrawal.
To facilitate early detection, reduce dosage periodically (if clinically possible)
and observe for signs of the disorder, especially since neuroleptics may mask
the signs of the syndrome.

References: 1. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc., 1980, p 415. 2. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 203, 221, 239.

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. The syndrome is characterized by hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal.

Phenothiazine derivatives have been known to cause restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occurs, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; epinephrine should not be used since phenothiazine derivatives have been found to reverse its action. Nausea, loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines. Local tissue reactions occur only rarely with injections of fluphenazine decanoate.

HOW SUPPLIED: Tablets—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100 and 500, and in Unimatic" carrons of 100. Elixir—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated dropper. Oral Concentrate—in bottles of 120 mL with calibrated dropper. Injection—in multiple-dose vials of 10 mL. Fluphenazine Decanoate—in 1 mL Unimatic" single dose preassembled syringes and 5 mL vials.

For full prescribing information, consult package inserts. (J4-120/147/153/150)

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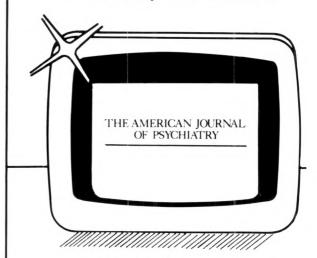
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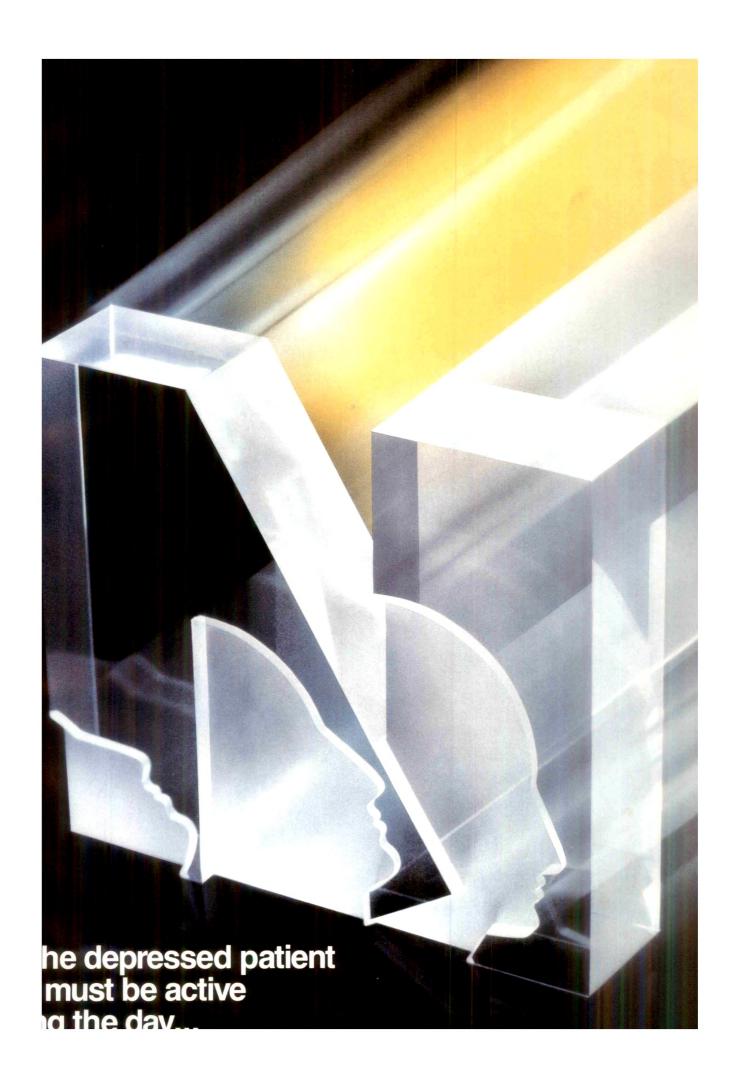


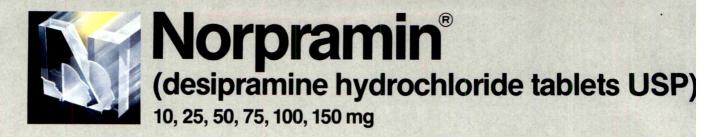
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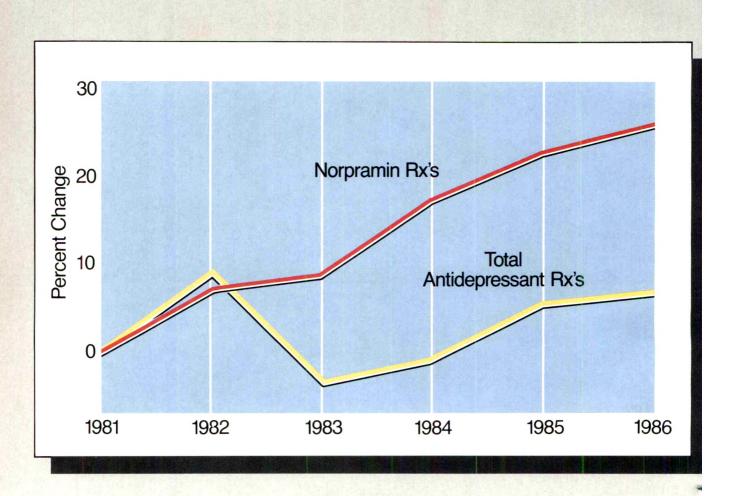


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**Brief Summary** 

Brief Summary

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic anti-depressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic anti-depressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic anti-depressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

serotonin re-uptake

serotonin re-uptake.

Norpramin (designamine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imigramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (designamine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

Ituli treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations. a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of uniary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with hyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of intrary retention or glaucoma, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. 2. This drug is capable of blocking the antihypertensive effect of quanethidine and similarly acting compounds. 3. USE IN PREG-NANCY: Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or wom

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since sui-

cide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. 2. If serious adverse effects occur, dosage should be reduced or treatment should be altered. 3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.

4. The drug may cause expectation of psychosis in schizophagois. Induce a hypomanic state after the depressive phase terminates.

4. The drug may cause exacerbation of psychosis in schizophrenic patients.

5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anti-cholinergic or sympathomimetic drugs.

6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.

7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited.

Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.

8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benemployed since the sedative effects of Norpramin and ben-zodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tran-quilizers are also additive to those of Norpramin. 9. This drug-should be discontinued as soon as possible prior to elective sur-gery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. 10. Both elevation and lowering of blood sugar levels have been reported. 11. Leukocyte and differen-tial counts should be performed in any patient who develops fever and sore throat during therapy: the drug should be discontinued if tial counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression. 12. Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (designamine hydrochloride) is

given.

<u>Cardiovascular</u>: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

<u>Psychiatric</u>: confusional states (especially in the elderly) with halucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of

Psychologic numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extra-pyramidal symptoms; seizures; alteration in EEG patterns;

tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adentitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dialation of urinary tract. Allergic; skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs. Hematologic; bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

black tongue

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar

levels.

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing, urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms; Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea headache, and malise.

sea, headache, and malaise.

DOSAGE AND ADMINISTRATION: Not recommended for use in children. Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for propried of time and sevelable as the lowest dose that will mantate. a period of time and should be at the lowest dose that will maintain

remission.

<u>Usual Adult Dose</u>: The usual adult dose is 100 to 200 mg per day.

In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased

according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECGs) are available.

(ECGs) are available. The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Initial therapy may be administered in divided doses of a singular daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

daily dose.

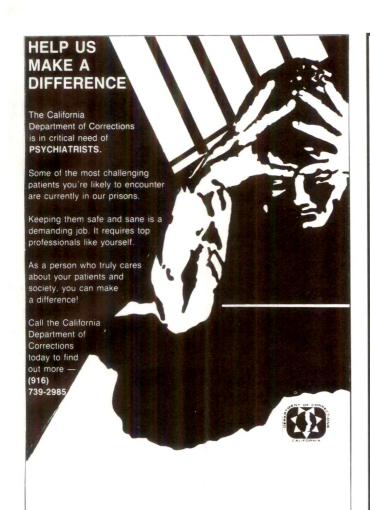
Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion of the second second second second second second sec symptoms and treatment of overdose

Product Information as of January, 1985

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## Merrell Dow



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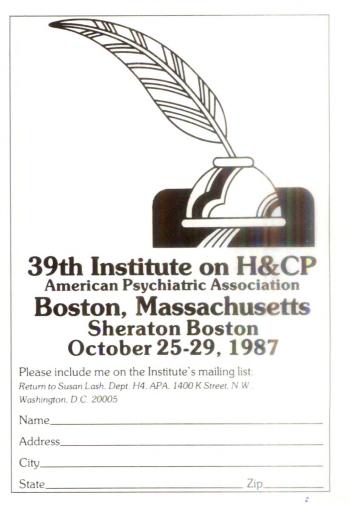
Further information may be obtained from:

The Secretary/Manager, St. Patrick's Hospital, at the above address,

to whom formal applications should be submitted before 30th October, 1987.

# **CLINICAL DIRECTOR**

The Department of Psychiatry at the University of Vermont and the Medical Center Hospital of Vermont is seeking a Clinical Director for inpatient services. The Clinical Director is a member of the full-time faculty. Applicants should be board certified and have prior experience in similar inpatient settings. The MCHV is the major teaching hospital of the College of Medicine and is a tertiary referral center for Vermont, northern New England and New York. Deadline for applications is November 30, 1987. Contact Sheldon Weiner, M.D., Professor and Chairman, Department of Psychiatry, UVM College of Medicine, Burlington, Vermont 05405. The University of Vermont is an affirmative action and equal opportunity employer. Women and minorities are encouraged to apply.



# **PSYCHIATRISTS**

The Southern California Permanente Medical Group, a multi-specialty group practice, is now accepting applications from General, Child, and Geriatric Psychiatrists who are board eligible/certified for outpatient positions at various clinics throughout Southern California.

Additionally, a General Adult/Adolescent Psychiatrist with bi-lingual Spanish skills is required for the inpatient Mental Health Center in Los Angeles.

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For additional information or a Physician Application form, call (818) 405-3224 or send your curriculum vitae and the names, addresses and telephone numbers of three professional references to:



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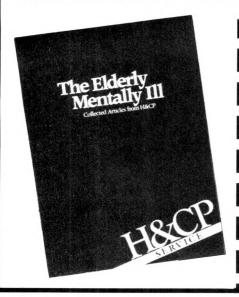
Send C.V. in confidence to: Richard C. Pillard, M.D.

Richard C. Pillard, M.D. Boston Psychiatric Group, P.C. 85 E. Newton St. Boston, MA 02118

# An essential resource for your library

The Elderly Mentally Ill: Collected Articles From H&CP offers you expert consultation from some of the nation's leading authorities on the planning and delivery of mental health services for the elderly. Published by the Hospital and Community Psychiatry Service, this helpful booklet contains 13 articles that present practical information and guidelines on subjects ranging from the development of hospital, community-based, and outreach and consulta-

tion services to prescribing psychotropic drugs, diagnosing and managing sleep disorders, and helping families cope with Alzheimer's disease. Contributors include Gene D. Cohen, M.D., Ph.D., Barry Reisberg, M.D. Charles M. Gaitz, M.D., Ben Gurian, M.D., Paul Teusink, M.D., and Nancy Mace, M.A. With an introduction by Dr. Cohen, director of the Program on Aging of the National Institute of Mental Health.



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# Psychological Medicine

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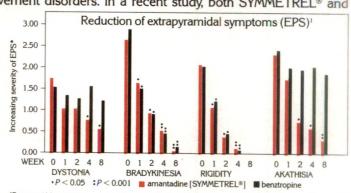


# rom the clutches of EPS

# Effective control of extrapyramidal symptoms (EPS)

SYMMETREL® (amantadine HCI) has been proven clearly effective in controlling a broad range of extrapyramidal movement disorders. In a recent study, both SYMMETREL® and

benztropine "were equally effective in treating druginduced parkinsonism; however, amantadine [SYMMETREL®] proved somewhat more effective in reducing akathisia and recurrent dystonia."



\*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p. 42

# Fewer side effects than anticholinergics

Dramatically differentiating SYMMETREL® from anticholinergics is its favorable side effect profile. With fewer anticholinergic side effects, SYMMETREL® affords patients greater com-

fort—encouraging compliance with their antipsychotic regimen. SYMMETREL® is not metabolized and is mainly excreted in the urine. Care should be taken, however, in patients with renal impairment. SYMMETREL®. The more rational and safer therapeutic choice in the control of EPS.

Incidence of anticholinergic side effects		
	% patients taking amantadine	% patients taking benztropine
Dry mouth	7.4	41.6
Blurred vision	2.6	26.5
Nasal congestion	2.5	18.2
Constipation	1.8	21.4
Urinary hesitancy	1.3	7.1

—adapted from Borison and Diamond, p 431



Please see following page for brief summary of prescribing information







BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions: SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levo-dopa, (-)-3-(3, 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs has than that observed with anticholinergic antiparkinson drugs. **CONTRAINDICATIONS:** SYMMETREL is contraindicated in patients with known

hypersensitivity to the drug

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be

followed closely as there are patients who developed congestive heart failure while

receiving SYMMETREL.
Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring

of vision should be cautioned against driving or working in situations where alertness

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension.

Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver

disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems

Pregnancy Category C: SYMBETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the letus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are: depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety; irritability; anorexia, nausea, and constipation; ataxia and dizziness (lightheadedness); livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After

medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary

daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for expenditure of the dose to 400 mg daily. Alternatively, temporary discontinuation of SYMMETREL for

dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMEL HEL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anti-cholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit parid thereafted the second part of the se

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit. When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

regain lost benefit with the addition of SYMMETREL. **Dosage for Drug-Induced Extrapyramidal Reactions:** Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

6043-15BSP/Rev. Oct. 1984

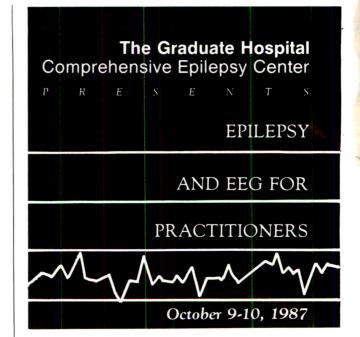
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REFERENCE: 1. Borison RL, Diamond Bl: Treatment of extrapyramidal side-effects: nantadine versus benztropine. World J Psychosynthesis (special), 1984-1985, pp 40-43



### Course Director: Marc A. Dichter, M.D., Ph.D.

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Credits: 13 CME Category I

Fee: \$200.00 (Refunds for cancellation prior to September 15, 1987)

05



# MENTAL TINESS AWARENESS WEEK

October 4-10, 1987

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Excellent opportunity for Board Certified Psychiatrist to provide management of drug dependent patients and to assume responsibility for supervision of clinical professional staff, including psychiatrists, physicians, social workers, activity therapists and substance abuse counselors. Serve on hospital committees, act as liaison to community agencies and conduct training and research. Salary commensurate with experience; \$66,959 to \$76,761, plus full state benefit package.

#### Staff Psychiatrist

Opportunities for a Staff Psychiatrist to participate in diagnosis, care and treatment of substance abuse patients and consultation to professional staff. Review work of nurses and other professional staff, instruct staff on individual clients and general ward medical management; prescribe therapies. Completion of a psychiatric residency training program approved by the American Board of Psychiatry and Neurology is required. Salary commensurate with experience; \$57,027, to \$63,163 starting, plus full state benefit package. Please send CV and requests for information to: J. Murtha, Personnel Officer I, Dutcher Chemical Dependence Treatment Center, Box 351, Middletown, CT 06457, or call, (203) 344-2537.

An Equal Opportunity Employer.

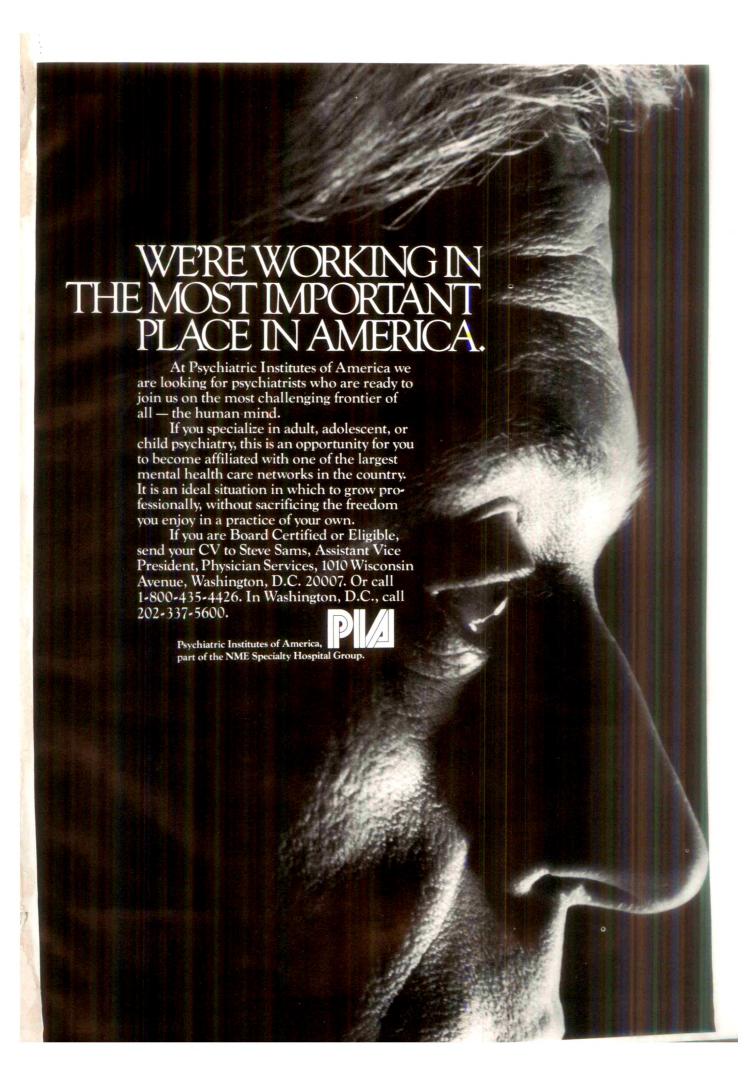


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#### **SEPTEMBER 1987**

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